# Financing translation: Analysis of the NCATS rare-diseases portfolio

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The portfolio of the National Center for Advancing Translational Sciences (NCATS) rare-diseases therapeutic development program comprises 28 research projects initiated at the preclinical stage. Historical data reveal substantially lower costs and higher success rates but longer preclinical timelines for the NCATS projects relative to the industry averages for early-stage translational medical research and development (R&D) typically cited in literature. Here, we evaluate the potential risks and rewards of investing in a portfolio of rare-disease therapeutics. Using a "megafund" financing structure, NCATS data, and valuation estimates from a panel of industry experts, we simulate a hypothetical megafund in which senior and junior debt yielded 5 and 8%, respectively. The simulated expected return to equity was 14.7%, corresponding to a modified internal rate of return of 21.6%. These returns and the likelihood of private-sector funding can be enhanced through third-party funding guarantees from philanthropies, patient advocacy groups, and government agencies.

The U.S. Food and Drug Administration's (FDA's) Office of Orphan Product Development (OOPD) defines an "orphan" rare disease as one that affects fewer than 200,000 U.S. patients. Although each rare disease has a low prevalence, an estimated 25 million to 30 million Americans are affected by the collection of more than 6800 rare diseases recognized by the U.S. National Institutes of Health (NIH). Globally, rare diseases affect ~350 million people and are responsible for 35% of deaths within the first year of life (1). Drug development for rare diseases poses a particular set of challenges, including small patient populations and diagnostic delays resulting from a lack of medical expertise and public awareness. Moreover, the small market size of individual orphan diseases and perceived lack of profitability have been barriers to private-sector investment in orphan drugs. To address these challenges, the U.S. Congress enacted the Orphan Drug Act of 1983, which provides incentives to sponsors of orphan drugs—including 7-year market exclusivity, tax credits equal to half of the devel-

opment costs, grants for drug development, and fast-track approvals of drugs indicated for rare diseases—and was later amended to include waiver of user fees charged under the Prescription Drug User Fee Act (PDUFA). Before 1983, only 10 new drugs for rare diseases were developed by the pharmaceutical industry (2), whereas according to the FDA database, 221 orphan-designated products received FDA approval over the decade ending 3 November 2014 (3).

Recent work by Fagnan et al. (4) shows that orphan drug development is particularly well suited to be financed through a megafund—a financial investment fund in which investors commit capital to be used for developing a portfolio of orphan drugs and receive the proceeds of these investigational drugs or intellectual property (IP) rights as they are sold to venture capitalists (VCs) or licensed by pharmaceutical companies. By diversifying the risk of drug development across many "shots on goal," the likelihood of success increases, and the financial risk-reward profile of an investment in the megafund becomes more attractive than that of any single project. The more attractive the megafund's returns are, the more likely it is that large amounts of capital can be raised to support such diversification. Using standard industry parameters for development costs, revenue projections, and historical success rates for orphan drug development, Fagnan et al. show that a portfolio of 10 to 20 projects can yield double-digit annualized returns with a $575 million megafund (4). However, their simulated results are based on industry

averages and anecdotal data and therefore may not be achievable in practice. In fact, one of the main challenges to adopting the megafund structure is the lack of a business model to manage such a fund; portfolio selection and project management require deep domain knowledge of both drug development and financial engineering.

In this article, we apply the megafund concept to analyze a real-life rare-disease portfolio from NIH's National Center for Advancing Translational Sciences (NCATS) (5). Two late-stage preclinical drug-development programs operated at NCATS's Division of Preclinical Innovations (DPI)—the Therapeutics for Rare and Neglected Diseases (TRND) and Bridging Interventional Development Gaps (BrIDGs) programs—are particularly relevant for providing a concrete example of a potential business model for an orphan drug megafund. Using pooled data from TRND and BrIDGs combined with industry averages from Fagnan et al. (4) for typical orphan diseases, we have constructed a more refined and realistic simulation of the performance of a hypothetical orphan drug megafund. Realized costs, timelines, and success rates are used to compute performance, and valuations for each project in the NCATS portfolio are obtained by averaging the assessments of a panel of independent industry experts.

Using the total horizon time of 11 years, we estimated that the average annualized returns of this hypothetical megafund range from 12 to 15%. Moreover, average internal rates of return measured on net cash flows—a metric typically used by venture capitalists—can be more than twice these raw annualized returns. NCATS data suggest substantially lower costs and higher success rates but longer preclinical timelines than the industry averages used by Fagnan et al. (4). In particular, the simulated performance of an NCATS rare-disease portfolio is comparable with that of a VC fund with an internal rate of return of more than 25%. The addition of debt tranches and a third-party guarantee of principal can increase the average raw return by 200 percentage points. Last, although the hypothetical megafund calibrated to NCATS data is simulated as a private enterprise, additional benefits could be obtained from a public-private partnership model.

## SELECTING PROJECTS

The TRND program within the NCATS DPI considers applications for projects in the translational medicine space in which

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the target disease qualifies for FDA's orphan product designation or is on the World Health Organization (WHO) neglected tropical disease list. TRND accepts projects with investigational drug candidates between the lead-optimization and investigational new drug (IND)–filing stages. In four years, TRND has taken four new molecular entities (NMEs) or repurposed drugs into the clinic for both phase 1 and phase 2 studies. The goal of TRND is to take projects to the earliest stage at which they are commercially attractive to private investors such as industry or VCs, who are able to take the commercialization process to completion. The TRND program also explores innovations aimed at improving preclinical success rates, managing risk, and reducing costs of advancing research breakthroughs into treatments, such as the development of platform technologies and new business models. The BrIDGs program focuses primarily on generating data for IND applications but is not limited to rare or neglected diseases projects. As with TRND, BrIDGs is not a grant-based program; successful applicants are provided with access to government contract resources to complete the IND-enabling studies required by FDA. For both the TRND and BrIDGs programs, the current NCATS operation model is to perform milestone activities sequentially; this means that subsequent milestone studies are initiated only after the preceding ones have been completed successfully. This sequential approach has been adopted largely because of a limited budget; with larger budgets, launching carefully selected key-project studies in parallel likely can shorten project timelines and enhance overall portfolio return.

NCATS hosts public solicitations to invite abbreviated applications to both programs, and selected applications are reviewed by a committee of external drug-development experts for scientific merit and technical feasibility. NIH discipline and disease experts then review top-tier applications for disease-specific merits. If selected, applicants are then requested to submit a complete data package and all relevant supplementary materials so that the TRND and BrIDGs staffs can conduct a detailed review under a standard confidentiality agreement. The final portfolio-selection decision balances several considerations, including disease area, currently available therapies, treatment modalities, stage of development, platform technologies, NCATS technical expertise and overall mission, and financial factors such as portfolio impact and budget.

Once a project is selected for the portfolio, a team consisting of both NCATS staff and applicant investigators is formed, and a detailed project plan is developed, including timelines, milestones, deliverables, and clearly defined quantitative go/no-go decision criteria. Milestones include lead optimization, completion of IND-enabling studies, IND filing, and phase 1 and phase 2 clinical trials. Project execution is guided under a three-tiered governance structure and managed by a project-team leader who has extensive industry drug-development experience. The project team has full autonomy to execute against the project plan without having to go through layers of approval for decisions. A joint research committee is formed to play a key role in providing technical feedback and suggestions to help the team during project execution. NCATS leadership is informed of program progress on a regular basis, and only changes to the plan's scope require additional NCATS approvals. When projects fail to meet a predetermined milestone, the TRND or BrIDGs project team will propose and conduct a closeout of the project and offer consultation and assistance to the applicants with respect to moving forward.

If a project meets all milestones, NCATS completes its investments and assists its partners in securing private investments from either pharmaceutical and biotechnology companies or VCs through various business-development activities. Among the 28 rare-disease projects at NCATS analyzed in this study, more than a third of the projects have obtained funding from other sources, including VCs, venture philanthropy, the NIH Clinical Center, and pharmaceutical companies.

## ANALYZING THE NCATS PORTFOLIO

Data were collected for 28 rare-disease projects—15 from TRND and 13 from BrIDGs, all selected before September 2013—that spanned a diverse range of therapeutic areas, including oncology (3), hematology (5), musculoskeletal diseases (5), cardiovascular diseases (2), central nervous system diseases (6), endocrine disorders (4), ophthalmology (2), and respiratory disorders (1). A complete list of the 28 projects is provided in table S4. Projects within BrIDGs that are not rare disease–focused were not included in our data set or analysis. For treatment modalities, there were 5 projects involving existing drugs repurposed for orphan indications, 13 NMEs, 8 large molecules (including antisense oligos, peptides, and biologics), 1 stem cell therapy, and 1 gene vector therapy. Collaborating organizations included 15 academic institutions, 9 small biotech companies, 3 NIH intramural laboratories or clinical groups, and 2 large pharmaceutical companies. The diversity of the portfolio in terms of therapeutic area, modality, and collaborating organization was designed to achieve maximum impact of limited program funding through "multiple shots on goal" as well as to help NCATS staff identify systemwide bottlenecks and develop models and tools to help improve the efficiency of the translational medicine pipeline.

The data cutoff date for our analysis was 31 December 2013, and included in the analysis were items such as the clinical and regulatory success or failure of observed transitions between established milestones, the durations of such transitions (including time spent active and on hold), and expenses incurred by NCATS and other project collaborators during each transition period. Within the 28 rare-disease projects, 20 were ongoing at this time, requiring measurement at intermediate milestones to capture the depth of the data. Twenty-four and four projects entered the NCATS pipeline at the IND-enabling phase and lead-optimization phase, respectively. Ten projects achieved at least one or more of the following milestone transitions: lead optimization ($n = 1$), IND-enabling ($n = 9$), IND filing ($n = 9$), initiation of phase 1 clinical trials ($n = 8$), and initiation of phase 2 clinical trials ($n = 5$). One project failed to reach any transition milestone. Additional success-rate data were obtained by including projects that were continued by collaborators after completion of the BrIDGs program, resulting in an additional five measured transitions from phase 1 clinical trials and three from phase 2. As a result of the small number of transition observations (1 to 10 depending on the parameter), we applied a weighted average using estimates drawn from the orphan drug literature (4) and prior belief weights. For example, we considered it unlikely that phase 2 projects would typically take 6 months, so for this parameter, we used a prior with increased weight (95%) on literature estimates. To provide a fair comparison, we combined the two IND phases that we associated with the preclinical phase in (4). Details of the other prior weights can be found in supplementary materials.

## VALUATION PANEL

In addition to data on the transition probabilities from one phase to the next, market valuations of the projects are needed to simulate investment returns. Previous studies have used industry averages to calibrate such simulations (*4*), but these averages are unlikely to reflect the singular aspects of the NCATS portfolio. Therefore, to provide valuation estimates for our 28 sample projects, we convened a panel of five industry experts, all of whom were active in the biotech industry and had a relevant mixture of past experience (in biotech, drug development, VC, and biotech investment banking) and job titles (including chief executive officer, company founders, managing partners, and vice president). We asked these professionals to provide valuation estimates for our 28 sample projects (Fig. 1). Our motivation for engaging these individuals was not only because of their deep expertise in biotech investing but also because they represented the most natural acquirers of NCATS portfolio projects; hence, even though their estimates may not be any more precise than those of other experts, their valuations are more practically relevant than are generic industry averages.

The data provided to the panel on the portfolio of projects included the collaborator organizations and disease-specific information (such as prevalence, incidence, and standard of care) but not information on realized costs and project stage durations. The panelists were asked to estimate the fair market value for each project in its current state and were given the option of providing up to three estimates: a low valuation, a best-guess valuation, and a high valuation. Results were sorted by project stage (using a log scale) (Fig. 1) [in contrast to the industry-average estimates in (*4*), which apply to the current phase only and are not based on any project-specific information]. Vertical bars represent the range of the low and high values provided by the respondents (*6, 7*), whereas the points represent their best guesses, which were taken to be the average of the high and low valuations if not explicitly specified. The range of estimates underscores the challenge of valuing early-stage translational medicine projects; any valuation of these projects is likely to yield highly speculative estimates of true economic value. In fact, one panelist prefaced his valuations with the caveat that his estimates should be treated as coarse approximations because normally, he would spend 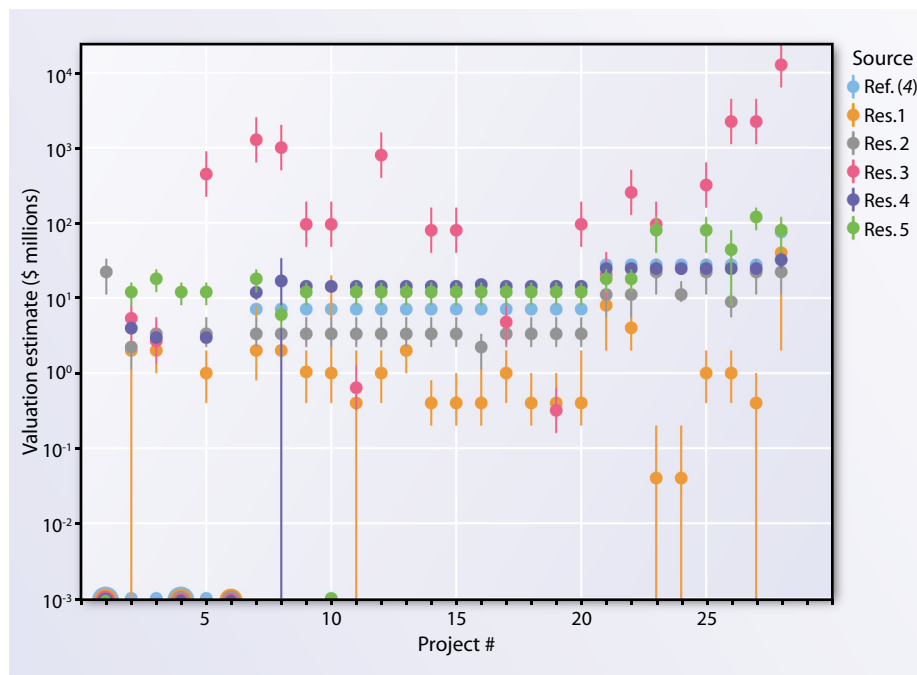substantial resources and weeks of time to determine the value of a single project (the full set of comments provided by the panel members is included in supplementary materials).

For the majority of projects, the best guesses of at least two panelists were higher than the corresponding estimates from the literature. The values of one panelist for some projects were orders of magnitude higher than those of the other respondents. To reduce the impact of these outliers and improve the accuracy of our estimates of market value, we used the median estimates among the five panelists rather than the maximum (which is what a typical bidding process would do). Last, in our simulation we captured the imprecision of valuing early-stage biotech projects by specifying a large standard deviation (more than 80% of the value of the mean) for the distribution from which we simulated our valuations.

## SIMULATION CALIBRATION

The megafund simulation model of Fagnan *et al.* (*4*) relies on several key model parameters (Fig. 2), including clinical trial costs, clinical trial durations, market valuations, and probability of technical and regulatory success. To calibrate these parameters for a simulation of a hypothetical megafund of rare diseases based on the NCATS data, we took a weighted average of the parameters used in (*4*) and the parameters obtained from the NCATS data using weights based on prior beliefs and knowledge about the NCATS process. We then used the medians of the valuation panel's estimates to compute the financial rate of return of NCATS projects by stage.

The impact of these calibrations results in lower costs and higher success rates for all phases, longer preclinical development times, shorter clinical development times, and lower economic valuations relative to literature averages from (*4*). The impact was greatest at the preclinical stage, for which we had the greatest number of observations, and was smallest at the phase 2 stage, for which fewer transitions were observed. Other simulation parameters were used as well, including pairwise correlations among asset valuations; probability distributions of costs, valuations, and stage
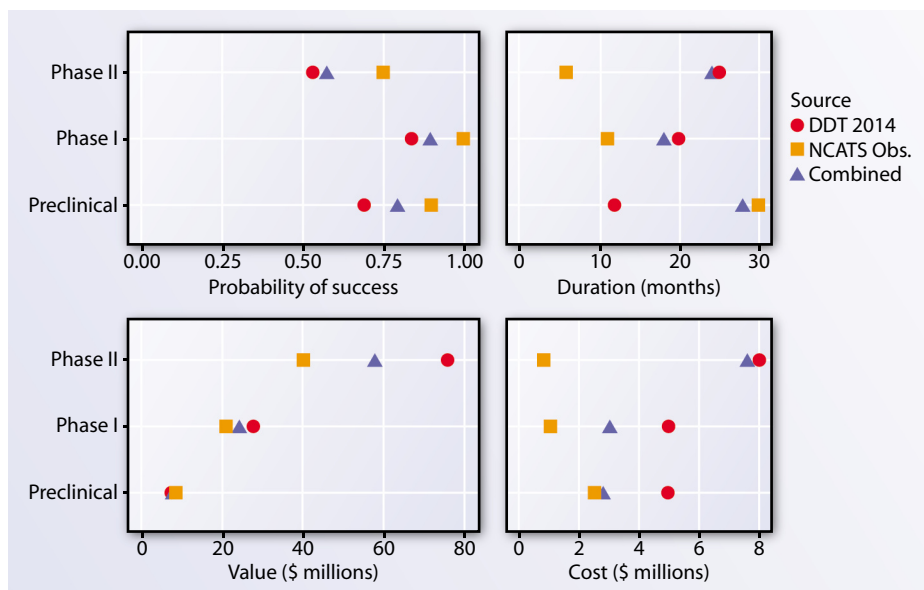


**Fig. 1. Value proposition.** Summarized are the valuation estimates (log scale), from panel members (selected by A.W.L.) for the NCATS rare-disease portfolio compared with literature estimates (*4*) based on project phase alone. Vertical bars represent the range of the panelists' lower and higher values. Projects are sorted by the stage at which they were valued, from lead optimization to phase 3 clinical trials. The responses of the panel members were formulated independently. The identities of panelists (who received no compensation or recognition for their participation) were not disclosed to each other or to NCATS personnel (including this article's NCATS coauthors), and minimal direction was provided on how they should complete their task (supplementary materials).

**Fig. 2. Simulation calibration.** Shown are weighted averaging of parameter estimates based on NCATS rare-disease portfolio, valuation panel, and literature estimates (*4*), using prior belief weights (methodological details are provided in the supplementary materials).

durations; upfront and milestone payments; and equity-sharing percentages (parameters and methodological details are provided in the supplementary materials). Using these additional assumptions and procedures, log-normal distributions were calibrated for project costs, valuations, and durations, and random draws from these distributions were simulated to generate the statistical behavior of megafund returns. Results for distributions other than log-normal are provided in the supplementary materials.

Although the NCATS data and valuation panel estimates provided more realistic values with which to calibrate the simulation parameters, obtaining accurate parameter values was challenging and required sustained collaboration between biomedical and financial experts. For example, a key set of inputs into these simulations was the pairwise correlation of market valuations among projects in the portfolio; although we specified a fixed value of 20%, in practice these correlations are likely to depend on the similarity of the underlying scientific pathways, mechanisms, and targets on which the projects are based. As more empirical research is published on the historical performance of individual biopharma investments, the estimation errors will be reduced. To facilitate this process, our simulation software is available online with an open-source license that allows others to use, modify, and redistribute it.

## MEGAFUND SIMULATIONS

Fernandez *et al.* (*8*) presented results of a detailed set of simulation experiments including stochastic phase transitions, correlations, and management of cash flows for future clinical trials. Their framework uses a multistate, multiperiod approach in which transitions occur according to a Markov-chain transition matrix and all costs and valuations are drawn from (capped) log-normal distributions. Investigational drugs are only given further investment for later-stage trials if there is sufficient capital for short-term debt-coupon and principal payments. If sufficient capital is not available, the compounds either are sold to cover debt payments or held until additional capital becomes available.

Fagnan *et al.* (*9*) extend this framework by analyzing the impact of third-party default guarantees for the debt tranches. Such guarantees can increase the attractiveness of research-backed obligations (RBOs) to both equity and bond holders with relatively low expected cost. More recently, Fagnan *et al.* (*4*) explore simulations focused on rare diseases, highlighting their suitability for inclusion in a megafund as a result of several factors, including higher chance of success, lower clinical costs, and faster average approval times.

We modeled the NCATS portfolio as a hypothetical private-sector megafund, ignoring any potential public-private partnership benefits and the value of new IP, such as

general translational medical expertise and patents generated by NCATS staff independently or jointly with collaborators. Following the approaches in (*8*) and (*4*), we considered an RBO structure consisting of a senior tranche, a mezzanine tranche, and an equity tranche. Because of the complexities of the debt-coupon and principal payments and the drug-approval process, numerical simulations were used to evaluate the financial performance of the RBO securities. We focused on early-stage investments, simulating the sale of preclinical projects upon completion of phase 2 clinical trials, if successful. This early stage represents a particularly challenging part of the drug-development process for which funding is scarcest and traditional financing models have struggled. In addition to the calibration of inputs discussed in the previous section, we made a key change from (*4*) by using a more realistic model for stochastic clinical times by use of a log-normal distribution, abandoning the Markov-chain approach used in many previous studies, which implicitly imposes a geometric distribution of stage duration (results for alternative distributions are provided in the supplementary materials).

The results of three sets of simulations using the NCATS rare-disease portfolio–calibrated parameters are shown in Table 1, with each set based on 2 million simulated paths. Each set of simulations acquires solely preclinical compounds, with the intent to carry the compounds through completion of a phase 2 trial. The first set of simulations consisted of an RBO structure in which the senior and junior debt tranches were assumed to pay 5 and 8% semiannual coupon rates, respectively. Using capital of $420 million ($189 million in debt, $231 million in equity), 16 preclinical compounds were acquired and funded. The second set of simulations consisted of an all-equity structure in which nine preclinical compounds were acquired by using a similar amount of equity capital ($230 million) as in the first simulation. The third set of simulations was similar to the RBO structure but contained the added feature of a third-party default guarantee for the junior debt tranche, protecting the principal of these bond holders in case of default. This guarantee has the effect of shifting the junior debt tranche into the senior tranche, yielding a single (senior) debt issue for the RBO structure. All three simulations used a maximum 11-year horizon, including a 6-month set-up time and 1 year for terminal liquidation of projects.

| Simulation results | All equity (similar equity) | Research-backed obligation (RBO) | RBO with guarantee (no mezzanine) |
|---|---|---|---|
| **Number of compounds** | | | |
| Preclinical or IND-enabling | 9 | 16 | 16 |
| **Research impact** | | | |
| Number sold in phase 2 | 0.4 | 1.9 | 1.6 |
| Number sold in phase 3 | 3.4 | 5.3 | 5.6 |
| **Liabilities** | | | |
| Capital ($ millions) | 230 | 420 | 420 |
| Senior tranche ($ millions) | — | 105 | 189 |
| Junior tranche ($ millions) | — | 84 | — |
| Equity tranche ($ millions) | 230 | 231 | 231 |
| Guarantee ($ millions) | — | — | 100 |
| **Equity tranche performance** | | | |
| Equity tranche performance | 3.25 | 5.14 | 5.32 |
| Average IRR | 26.7% | N/A | N/A |
| Average MIRR (0% financing) | 18.3% | 21.6% | 22.7% |
| Average annualized ROE | 11.6% | 14.7% | 15.4% |
| Probability (equity wiped out) | 1.3 bp | 0.52% | 0.34% |
| Probability (return on equity <0) | 8.0% | 6.2% | 5.1% |
| Probability (return on equity >10%) | 61.9% | 76.8% | 78.6% |
| Probability (return on equity >25%) | 2.2% | 10.4% | 11.0% |
| **Debt tranches performance** | | | |
| Senior tranche: default probability, expected loss (bp) | — | 0.1, <0.1 | <0.1, <0.1 |
| Junior tranche: default probability, expected loss (bp) | — | 50, 15 | — |
| **Guarantee performance** | | | |
| Probability (cost of guarantee >0) | — | — | 0.3% |
| Expected cost, 2% discount ($) | — | — | 65,000 |
| No-arbitrage cost of guarantee ($) | — | — | 110,000 |

**Table 1. Structure and function.** Simulated performance comparing an all-equity structure (using no debt financing); an RBO structure using a senior and junior debt tranche paying 5 and 8% annual coupon rates, respectively; and a second RBO structure with a single guaranteed senior tranche. The senior tranche is paid before the junior (mezzanine) tranche, which is paid before the equity holder. In the event that the fund defaults or fails to meet its debt obligations, the guarantor will pay the difference. Each structure acquires only preclinical compounds, with a target goal of reaching phase 3 within a maximum horizon of 11 years. Dashes indicate cases in which the corresponding type of financing and/or guarantee is not used. IRR, internal rate of return; ROE, return on equity.

In addition to the performance metrics used in (4), we included two other metrics in order to provide a more detailed comparison. Motivated by industry practice, we included the mean raw return, with no discounting performed (for example, a mean raw return of 2.0 would mean that for every $1 of equity capital committed, an average of $3 was returned at the end of the simulation). In addition to the internal rates of return for the all-equity simulation, we included the modified internal rates of return (MIRR) on net cash flows, for which the financing rate for negative cash flows was set to zero. The MIRR

was computed by fixing the financing rate at zero and solving iteratively until the average MIRR equaled the (forward) reinvestment rate (supplementary materials).

As shown in Table 1, the average annualized return on equity for the all-equity model is 11.6%; this corresponds to a substantially higher internal rate of return of 26.7%, resulting from the possibility of equity holders receiving cash payments sooner than at the end of the 11-year horizon. By adding senior and junior debt of $105 million and $84 million, respectively, the average annualized equity return was increased to 14.7%, with

a corresponding MIRR of 21.6%, which is higher than the 18.3% MIRR simulated for the all-equity model. Although it is useful for comparison, the MIRR might not be a realistic performance measure for a structure with debt because the full amount of capital might need to be held as collateral.

Also shown in Table 1, the default risk to the bonds is quite low, with a <1 basis point default rate on the senior tranche, which is comparable with the historical performance of bonds with the highest credit ratings. Ignoring discounting, the average benefit to equity holders when bonds are also used to

finance the megafund was an almost twofold increase over the initial equity investment.

As a result of the increased amount of capital and larger number of projects, the probability of loss to the equity tranche for the RBO structure was only 6.2%, compared with 8.0% for the all-equity model. The use of debt also increased by a factor of nearly 5, and the probability of annualized returns was in excess of 25%. Moreover, this financing structure yielded an additional 1.9 projects completing phase 2 trials as compared with an all-equity model that used a comparable amount of equity capital.

A further increase in returns can be obtained by the addition of a third-party guarantee of $100 million, presumably provided by either a government agency or a philanthropic organization. Specifically, we considered a guarantee that had the effect of combining the two debt tranches into one single senior tranche paying a 5% coupon rate. In addition to potential fundraising benefits and higher bond ratings, the impact of this guarantee on equity returns was substantial, increasing the average annualized return on equity from 14.7 to 15.4%. Despite the high face value, the expected discounted cost to the guarantor was quite small, at $65,000, with an estimated Black-Scholes price of $110,000 (details are provided in the supplementary materials).

A sensitivity analysis of these results is provided in the supplementary materials, in which we describe the same simulation experiments conducted under a variety of different parameter values. One illustrative example used a 15% relative decrease in success probabilities at each project stage, which caused the simulated return on equity for the RBO to drop from 14.7 to 10.6%—still an attractive investment in the current economic climate. Moreover, under this alternate specification the default risk to the senior bond did not increase, whereas the junior bond default rate increased by only 18 basis points.

## BREAKING WITH TRADITION

In response to the growing consensus that traditional models for financing drug discovery are inadequate, a number of alternate business models and funding structures have emerged. Although drug royalty companies such as Royalty Pharma (10) have achieved financial success in funding later-stage drug development, they have not yet played a large role in the earlier stages. And despite promising simulation results,

the megafund structure has yet to be implemented in practice. The NCATS portfolio of rare-disease therapeutics provides a live example with which to calibrate megafund simulations for orphan drug portfolios.

At the time of this analysis, the NCATS rare-disease portfolio has been in operation for only 4 years; hence, none of the portfolio projects has reached FDA approval. Nevertheless, the combination of NCATS data and industry averages allows us to provide an interim financial analysis of the viability of the megafund structure for financing early-stage translational medicine research involving rare diseases. Our simulations show that a rare-disease megafund based on the NCATS business and operation model could achieve average annualized returns from 12 to 15% depending on the debt structure and with substantially higher internal rates of returns, a metric often used by the VC industry. The issuance of a guarantee on the debt can increase clinical impact per dollar of equity, return on equity, and fundraising potential for the debt. In particular, the average impact of adding guaranteed debt to the traditional all-equity model is an increase in the total cash payout to equity holders of twice their initial equity investment.

These simulation results must be qualified by the caveat that they are only simulations—not actual investment returns—and are based on a large set of assumed parameter values, some of which can be specified only imprecisely. For example, a key driver of the market value of candidate drugs is the cumulative sum of their future potential sales, and it is well known that drug sales are notoriously difficult to forecast (6). Scientists are often dismayed by the inaccuracy of financial forecasts, which are sometimes orders of magnitude more uncertain than the outcomes of laboratory experiments. This imprecision is an unavoidable feature of financial investments of all types, including biotech; nevertheless, investors continue to invest in the stock market despite comparably inaccurate forecasts of corporate earnings (11). Recent examples of other uncertain investments for which the methods described in this paper have been successfully applied include music royalties, Hollywood films, and the future earnings of professional athletes. In each of these cases, investors understand the limitations of historical and simulated performance metrics and are, nevertheless, willing to invest as long as they have some sense of what that

uncertainty entails [for example, the credit analysis underlying the securitization of film rights (7)]. The analysis presented in this article and our open-source software are intended to address this need for the biopharma industry.

The use of NCATS data to calibrate our simulations and as a template for an orphan-disease megafund might also seem optimistic at best, given the dearth of evidence regarding the economic impact of this fledgling organization. However, on 9 July 2014 the NCATS rare-disease portfolio collected a pair of data points: Two of its portfolio partner-companies were independently acquired by large pharmaceutical companies. AesRx, LLC, was acquired by Baxter International, Inc. ($15 million upfront, up to $278 million and $550 million in future development/regulatory and sales milestone payments, respectively), and BIKAM Pharmaceuticals was acquired by Shire ($2.5 million upfront, up to $92 million in future development/regulatory/ sales milestone payments). As with most biopharma acquisitions, even these observable market transactions are not trivial to value because of the many contingent payments that are triggered by confidentially specified events. However, a crude but commonly used (12) approximation of the economic value of these transactions can be computed by measuring the 1-day impact on the stock prices of the acquirers when these deals were announced on 9 July 2014: $238.3 million for Baxter and $423.1 million for Shire (supplementary materials), for a total of $661.4 million. As noisy as these estimates are, they provide the most current commercial assessment of the potential economic value generated by the NCATS rare-disease portfolio.

The fact that NCATS does not use financial return as a metric of its success suggests that our simulated megafund returns are conservative estimates of what can be achieved by a purely profit-driven private-sector institution. This nonfinancial motivation is embedded in both project selection and the operation of the TRND and BrIDGs programs. For example, some TRND applications were selected solely on the basis of the severity of unmet medical needs, even though the applicant did not have IP ownership of the proposed investigational drugs. This selection bias increases the risk that certain NCATS projects may never attract commercial interest from the private sector, which could substantially re-

duce the economic valuation of the NCATS rare-disease portfolio. Operationally, approaches are taken by NCATS to ensure the maximum success rate at the lowest cost to taxpayers by launching key project studies sequentially at the preclinical stage, which increases the average time to IND relative to running key project studies in parallel to accelerate the speed to proof of concept, a common industry practice. In practice, a megafund would apply more sophisticated financial analytics to balance the cost of multiple projects and project-related studies against the benefits of higher success probability so as to achieve the best risk-adjusted return for investors. Because of the complex and dynamic nature of drug development—which requires deep domain expertise at every step of the portfolio management process—we postulate that building shared drug-development infrastructure within a megafund can maximize operational efficiency and enhance the fund's risk-adjusted return.

The NCATS TRND and BrIDGs programs underscore the fact that translational science is a team endeavor, and rare-disease research, in particular, relies heavily on academia, the biotech and pharma industries, patient communities, advocacy groups, regulators, and government support (through both NIH and legislation). The ability to tap into resources from these various stakeholders can save tremendous amounts of time and money by ensuring that the right studies are designed and conducted, the right patient populations are recruited, and the proper regulatory guidance is obtained at the earliest relevant time. Such a business model, supported by the appropriate private-sector financing structures, can

help the translational medicine community traverse the translational Valley of Death.

## SUPPLEMENTARY MATERIALS

www.sciencetranslationalmedicine.org/cgi/content/full/7/276/276ps3/DC1

Table S1. Observations of NCATS rare-disease projects including success, duration, and cost of trials.

Table S2. Prior weight given to literature data for orphan diseases (4), with lower values relying more on the NCATS observations.

Table S3. Posterior estimates of parameters for simulating an NCATS rare-disease megafund, combining literature estimates for orphan diseases (4).

Table S4. NCATS portfolio of rare-disease projects in TRND and BrIDGs.

Table S5. Summary of key comments from valuation panel respondents when asked to value a portfolio of rare-disease projects within NCATS.

Table S6. Panel median valuations compared with literature estimates for orphan diseases (4).

Table S7. Parameters and distributions used in simulation framework for an NCATS rare-disease megafund.

Fig. S1. Plot of density functions for various Phase 2 clinical trial time distributions calibrated by matching first and second moments.

Table S8. Performance metrics for RBO structure (without guarantee) from Table S2 for alternative clinical trial time distributions.

Table S9. Calibrated parameters for valuation distributions at phase 3.

Fig. S2. Plot of density functions for various Phase 3 valuation distributions calibrated using first and second moment matching.

Table S10. Performance metrics for RBO structure (without guarantee) from Table S2 for alternative valuation distributions.

Table S11. Performance metrics for RBO structure (without guarantee) from Table S2 for adjusted probability of success applied to all stages.

Fig. S3. Performance metrics for RBO structure (without guarantee) from Table S2 for adjusted probability of success applied to all stages.

Fig. S4. Performance metrics for RBO structure (without guarantee) from Table S2 for adjusted mean and standard deviation of Phase 3 valuation.

Table S12. Performance metrics for RBO structure (without guarantee) from Table S2 for adjusted mean and standard deviation of Phase 3 valuation.

Fig. S5. NCATS rare disease portfolio diversity by disease and drug modality.

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