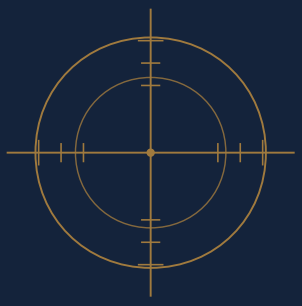
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WHITE PAPER · NOVEMBER 2026

The *Valley of Death*

Why the world's most important research dies on campus, and the commercial opportunity hidden in plain sight

Lawrence Fine
CEO and Co-Founder, AGCP Farmacêuticos

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PREFACE

About this paper

This whitepaper was written for three audiences who rarely read the same document: **policymakers and university administrators** wrestling with a historic contraction in federal research funding; **entrepreneurs, operators, and investors** who recognize that the contraction is also an opening; and **academic researchers** whose life's work will reach patients and markets, or will not, depending largely on decisions being made right now.

The argument is evidence-driven and globally scoped. It draws on data from AUTM, the NIH, NSF, the European Research Council, OECD, WIPO, peer-reviewed journals including *Nature*, *Science*, *JAMA* and *Nature Reviews Drug Discovery*, and primary reporting from *STAT*, *Science News* and others. Where sources disagree, I have said so. Where data is self-reported or contested, I have flagged it. This edition was revised in November 2026, and every reference was re-checked against its original source.

Disclosure: I am the CEO of AGCP Farmacêuticos LDA, a Lisbon-based nanotechnology pharmaceutical company with a reformulation platform for poorly soluble compounds. Two AGCP assets — our internal development platform and the PharmaSim training simulations, both part of the Graticus software suite — appear in this paper as illustrations of the kind of tooling and skills infrastructure that the Valley of Death has historically lacked. I have tried to frame them as examples, not advertisements. Readers can judge for themselves whether I have succeeded.

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OVERVIEW

Executive summary

In fiscal year 2025, US universities and research institutions reported **28,278 new invention disclosures**, filed **13,729 new US patent applications**, received **7,827 US patents**, executed **10,277 licenses and options**, and formed **1,095 startups**. In the same year, **761 new commercial products** reached the market. Products launched in a given year usually come from inventions disclosed years earlier, so this is a comparison of flows rather than a tracked conversion rate — but the order of magnitude is clear: for every hundred inventions recorded, fewer than three new products appear.

The picture in biopharma is starker still. Of drug candidates entering Phase 1 clinical trials, **only 6.7 percent reach approval** — down from 10.4 percent in an analysis published in 2014. Published estimates of the cost of developing a new drug range from about $880 million to $2.7 billion, depending on methodology. And by widely cited estimates, **up to 90 percent** of molecules in discovery pipelines are poorly water-soluble — meaning they are hard for the body to absorb in their native form, and many will never reach a patient unless someone reformulates them.

This paper calls that gap — between the discovery and the product, between the grant and the patient — by its common name: the *Valley of Death*. It is not a metaphor. It is a structural feature of how the world does research, and it has been widening for decades. Eroom's Law, the biopharma equivalent of Moore's Law in reverse, describes the number of new drugs approved per billion dollars of R&D halving roughly every nine years since 1950.

What 2025–2026 changed

The Valley of Death has been a chronic problem. In 2025 it became an acute one. NIH attempted to cap indirect cost reimbursement at 15 percent, a policy the courts blocked. More than 3,800 NIH and NSF research grants were terminated or frozen during the year, affecting roughly $3 billion in unspent funds; NSF alone listed 1,752 terminated grants worth $1.4 billion by May 2025. An opt-in *Nature* reader poll in March 2025 found that three-quarters of US-based respondents were considering leaving the country. European Research Council Starting Grant applications for the 2026 call rose **22.4 percent** over the previous call, which had itself risen 13 percent.

At the same time, other research systems are moving. The EU launched a €500 million "Choose Europe for Science" package for 2025–2027, and France added €100 million. The UK set public R&D investment at £86 billion through 2029/30. Singapore's RIE2030 plan commits S$37 billion. Portugal merged its science and innovation agencies into a single new body, AI², at the end of 2025. The world's research capital is reallocating, and the institutions that can absorb, develop, and commercialize it are being chosen right now.

The argument of this paper

I argue four things:

1. **The Valley of Death is a structural failure, not a funding failure alone.** The gap between academic discovery and commercial product persists even in well-funded research systems because of misaligned tenure incentives, weak commercial skills, fragmented IP structures, missing regulatory strategy, and a near-total absence of operational tooling at the translational stage.

2. **The 2025–2026 US contraction is a historic dislocation, not a cyclical one.** It differs from the 2013 sequestration or the 1995 budget fight in kind, not degree: the dismantling of USAID, topic-based mass grant terminations, university-by-university funding freezes, and an attempted indirect cost cap that the courts blocked. The effects on global talent and IP flows are likely to last for years.

3. **The opportunity is largest for operators who bring tooling and training, not capital alone.** Universities are not short of ideas or of capital in the abstract — they are short of the operational infrastructure that makes research licensing-ready and the commercial skills that make researchers investable. Data rooms, regulatory intelligence and patent analytics are standard equipment in industry deal-making, and simulation-based training has a strong evidence base. Very few universities have them integrated.

4. **Reformulation is an undervalued front.** Up to 90 percent of molecules in discovery pipelines are poorly water-soluble. Between 2010 and 2020, 570 of the 1,001 new drug applications the FDA approved — 57 percent — used the 505(b)(2) pathway, which lets a developer build on existing data for an approved drug; one industry analysis estimated an average five-year return of about 26 times R&D spend for 505(b)(2) launches. Celgene paid $2.9 billion for the developer of Abraxane. EXPAREL generated $538 million in 2023 net sales. Doxil waited 17 years for its first FDA-approved generic. The compounds sitting in academic labs — silibinin, berberine, paclitaxel analogs, ketoprofen and hundreds more — are the raw material of this next wave.

The fifteen-year window to reshape the global translational landscape has opened. This paper is about what is in that window, who is already building for it, and what it takes to cross the Valley of Death in both directions — from bench to market, and from capital to discovery.

SECTION 01

The funnel that leaks at every stage

1.1 The canonical definition, and why it matters

The phrase *Valley of Death* has been used in US science policy since at least 1998, when the House Science Committee's report *Unlocking Our Future* applied it to the gap between basic research and industry-driven product development. It became common currency in biomedical research a decade later. Declan Butler's 2008 *Nature* news feature, "Translational research: crossing the valley of death," described a widening gap between biomedical researchers and the patients their discoveries are meant to serve. Coller and Califf, writing in *Science Translational Medicine* in 2009, described the valley as the rough terrain between basic discovery and useful therapy in which many projects perish, and offered a framework for assessing a project's chances of crossing it.

Since then, the phrase has done real work. It has given research administrators, VCs, and policymakers a shared vocabulary for a specific kind of failure — one that is not about bad science or bad markets in isolation, but about the seam between them. Seyhan, reviewing the field in 2019, described the rift between bench and bedside as widening and deepening, and named poor hypotheses, irreproducible data, weak preclinical models, missing academic incentives and limited data sharing among the culprits.

Fernandez-Moure, in a 2016 bioengineering review, argued that funding and publication pressures have pushed both clinicians and researchers away from time-consuming translational work. It is also useful to separate **two valleys**, not one. The first is the gap between discovery and a license or Series A. The second is the gap between early human trials and revenue. Both kill projects. They have different causes and require different solutions. A paper that conflates them will recommend the wrong tools.

1.2 The funnel in numbers

The most widely used data on US university commercialization comes from AUTM, the Association of University Technology Managers. Its 2025 Licensing Activity Survey reports the following for US universities and research institutions:

STAGE	US INSTITUTIONS, FY2025
Research expenditures	**$112 billion**
Invention disclosures	28,278
New US patent applications	13,729
US patents issued	7,827
Licenses and options executed	10,277
Startups formed	1,095
New commercial products	**761**
Startups still operating (formed in any year)	6,990

Read top to bottom, the ratios tell a hard story. Issued patents equal roughly 28 percent of the year's disclosures; new products, under 3 percent. That works out to roughly $147 million of research spending for every new commercial product. These are flows rather than tracked conversions, but the pattern has been similar across recent AUTM surveys: the conversion rate has been low for a generation. One row works differently from the others. Every other figure counts activity within the single year; "startups still operating" is a running total — the number of startups formed by responding institutions, in any year, that were still in business at the end of FY2025. It has roughly doubled since FY2009, when AUTM reported 3,423, reflecting both a higher rate of startup formation and the fact that many survive for years.

What the cumulative numbers also show, to Bayh-Dole's credit, is that when research *does* translate, the returns are extraordinary. An AUTM–BIO analysis published in June 2022 estimates that from 1996 to 2020, university and nonprofit inventions contributed up to $1.9 trillion to US gross industrial output and up to $1 trillion to GDP, and supported up to 6.5 million jobs; more than 200 drugs and vaccines have been developed through public-private partnerships since the Bayh-Dole Act took effect. The issue is not that the funnel produces nothing. It is that the funnel wastes an enormous volume of potentially useful work at every stage.

1.3 Biopharma: the deepest valley

Biopharma has the worst attrition profile of any major research sector, and it is getting worse, not better. Hay and colleagues, writing in *Nature Biotechnology* in 2014, reported a Phase 1-to-approval likelihood of 10.4 percent for drugs tracked from 2003 to 2011. A BIO, Informa and QLS analysis of 2011–2020 lowered the figure to **7.9 percent**. Citeline's analysis of 2014–2023 put it at **6.7 percent**, with oncology at just 4.7 percent and respiratory at 4.5 percent.

Cost estimates span a wide range, depending on method and data. DiMasi and colleagues at Tufts estimated $2.56 billion per approved drug (2013 dollars) in a 2016 *Journal of Health Economics* paper based on confidential company data, or $2.87 billion including post-approval R&D. Wouters, McKee, and Luyten, using public SEC filings in JAMA in 2020, put the median at $985 million and the mean at $1.3 billion. Mulcahy and colleagues, in a *JAMA Network Open* analysis of 2019 approvals published in January 2025, reported a median of $708 million and a mean of $1.31 billion. Sertkaya and colleagues, also in *JAMA Network Open* (June 2024), estimated a mean out-of-pocket cost of $172.7 million, rising to $879.3 million once failures and capital costs are included. Deloitte's annual tracker of the 20 largest biopharma companies put the average cost per asset at **$2.23 billion in 2024 and $2.67 billion in 2025**.

The methodological differences matter, but the direction is consistent: success rates are falling and costs are high. And academic discoveries rarely make the journey alone. Takebe and colleagues, studying 798 drug discovery projects at 36 US academic institutions between 1991 and 2015, found collaboration with industry to be of significant importance to the projects that advanced.

This is Eroom's Law — Moore's Law spelled backward, named by Scannell and colleagues in a 2012 *Nature Reviews Drug Discovery* paper. The number of new drugs approved per billion dollars of industry R&D has halved roughly every nine years since 1950, an eighty-fold decline in inflation-adjusted terms. Scannell identified four causes: the "better than the Beatles" problem (new drugs must outperform increasingly effective predecessors), the cautious-regulator problem, the tendency to throw money at difficult problems, and the "basic research–brute force" bias of overinvesting in early-stage technique without sufficient validation. In a 2020 follow-up, Ringel, Scannell and colleagues reported that the trend appears to have broken after 2010, with productivity improving — though whether the improvement will last remains an open question.

1.4 The reproducibility crisis nobody has solved

Beneath the funnel sits a more uncomfortable fact. A significant fraction of the academic preclinical literature on which downstream development depends cannot be reproduced.

Begley and Ellis, writing in *Nature* in 2012, reported that scientists at Amgen had attempted to confirm 53 "landmark" preclinical cancer studies and succeeded in only **six — eleven percent**. Prinz, Schlange, and Asadullah, working at Bayer and publishing in *Nature Reviews Drug Discovery* in 2011, reported that in only 20 to 25 percent of 67 in-house target-validation projects were the published data fully in line with Bayer's own findings; in almost two-thirds, inconsistencies led to project termination. The Reproducibility Project: Cancer Biology, reporting in *eLife* in 2021, was able to complete 50 experiments from 23 high-impact papers; for positive effects, the median replication effect size was 85 percent smaller than the original, and only 46 percent of the

replications succeeded on more criteria than they failed. Freedman and colleagues in 2015 estimated that roughly $28 billion a year is spent in the US on preclinical research that is not reproducible.

> *"Even knowing the limitations of preclinical research, this was a shocking result."*
>
> C. Glenn Begley and Lee Ellis, Nature, 2012

The methodological critiques of these reproducibility studies are real — Amgen and Bayer did not publicly identify the specific papers they tried to replicate, and their selection criteria were not peer-reviewed — but the directional finding is now widely accepted across the field.

This matters for the Valley of Death because it means the funnel's early stages are even leakier than the numbers suggest. A disclosure based on a finding that does not replicate is an invention that cannot be licensed, a patent that cannot be defended, a startup that will fail at Phase 2.

1.5 The poorly soluble drug problem

One specific mechanism of failure inside the biopharma valley deserves special attention because it represents both the problem and a concentrated opportunity. Most new drug candidates are poorly soluble — classified as BCS Class II (low solubility, high permeability) or Class IV (low solubility, low permeability). Bhalani and colleagues, in a 2022 review, report that about **70 percent** of new drug candidates show low aqueous solubility; Kalepu and Nekkanti estimate that nearly **90 percent** of molecules in the discovery pipeline are poorly water-soluble, along with about 40 percent of marketed drugs.

In plain terms: an enormous number of potentially active molecules sit in academic laboratories and industry pipelines *specifically* because nobody has figured out how to get them into the body. Silibinin, with established activity in liver disease, is poorly soluble. Berberine, with documented activity in cardiovascular and metabolic disease, has very low oral bioavailability. Paclitaxel, before Abraxane, depended on the toxic solvent Cremophor. Curcumin, resveratrol, itraconazole, fenofibrate and many vitamin D analogs all face versions of the same problem.

The commercial point of this paper is that this is a *solvable* problem. Nanoemulsion, lipid nanoparticle, nanocrystal, solid dispersion, self-emulsifying drug delivery, and cyclodextrin-complexation approaches have all been used to rescue compounds from the Class II/IV trap. Abraxane — a nanoparticle albumin-bound formulation of paclitaxel — was the centerpiece of Celgene's $2.9 billion acquisition of Abraxis BioScience in 2010. Doxil, the first FDA-approved nanomedicine (1995), did not face an FDA-approved generic until 2013. The downstream market is measured in tens of billions.

The Valley of Death is not uniform terrain. It has specific weak points, and the poorly soluble drug problem is one of the most productive places to put a bridge.

SECTION 02

Why research dies: seven root causes

The funnel leaks for reasons. Understanding them matters because the remedies differ. A paper proposing more capital will not fix an incentive misalignment. A paper proposing tenure reform will not fix a regulatory knowledge gap. Below are the seven most commonly cited structural causes, each documented in the peer-reviewed literature and each addressable with a specific kind of intervention.

2.1 Tenure does not reward commercialization

The most consequential cause is also the most structural: most universities do not count commercialization toward tenure. Stevens, Johnson, and Sanberg, in a 2011 survey published in *Technology and Innovation*, found that **75 percent of responding institutions did not include patents or commercialization in tenure and promotion criteria**; they identified only 16 universities in the US and Canada that did.

Texas A&M was the first major US university to formally add commercialization as a "sixth factor" in tenure review, in May 2006. Sanberg observed in 2012 that, surprisingly, other major institutions had not followed A&M's lead. In 2014 he and seven other university leaders made the case again in PNAS. The pattern has not meaningfully shifted since.

> *"There is a fundamental disconnect between technology transfer activities and incentives for faculty members in terms of merit raises, tenure and career advancement."*
>
> Richard B. Marchase, co-author, PNAS 2014

This matters because a PhD-level scientist in year three of a tenure-track position responds, rationally, to the incentives they can see. Those incentives, almost universally, are: publish in high-impact journals, secure new grants, teach, serve on committees. Disclosing an invention and spending eighteen months on an SBIR application does not help them get tenure. In many departments, it still carries a mild stigma. The cumulative effect is that the researchers most capable of generating commercially valuable IP are also the ones least incentivized to pursue it.

2.2 Researchers lack commercial skills

Even when the incentives align, the skills often do not. The typical PhD trajectory produces a researcher with deep domain expertise, strong experimental design skills, and almost no training in market sizing, regulatory strategy, IP portfolio construction, financial modeling, or business

development. Kahn and Ginther, writing in *Nature Biotechnology* in 2017, found that for the roughly 80 percent of biomedical postdocs who do not reach tenure-track jobs, the postdoc does not raise later salaries, and that most would have been financially better off taking a job straight after the PhD. Khan and Casello, in a 2023 *Nature* career column, argued that because tenure is out of reach for most postdocs, they need entrepreneurship and business skills to thrive outside academia.

This is where training interventions matter. NIH's I-Corps program, adapted from Steve Blank's Lean LaunchPad methodology, takes academic teams through structured customer discovery. Meta-analyses of simulation-based training in related professional fields (Sitzmann 2011 in *Personnel Psychology*; Cook et al. 2011 in JAMA) show meaningful learning gains: Sitzmann's pooled analysis of 65 studies and 6,476 trainees found that those taught with computer-based simulation games scored 20 percent higher on self-efficacy, 11 percent higher on declarative knowledge, and 14 percent higher on procedural knowledge than comparison groups.

The skills gap is not unfixable. It is, however, systematically unaddressed in the typical PhD program.

2.3 Capital disappears at the translational stage

The third structural problem is a funding gap that sits exactly where it hurts most — between the end of an NIH R01 and the beginning of a Series A. Grants pay for basic research and industry pays for late-stage development, but the translational work in between — the experiments that de-risk a discovery enough for a company to license it — has neither a natural payer nor a natural home. This is the stretch Coller and Califf described as the valley itself.

Proof-of-concept funds designed to fill that middle have, when well-structured, worked. In its first five years, the University of Michigan's Coulter Translational Research Partnership funded 19 projects, which produced four startups and drew $25 million in follow-on support. Programs like this are not common. Most universities do not operate a translational gap fund of their own, and the SBIR/STTR programs that have historically filled part of the role lapsed on October 1, 2025 and were not reauthorized until April 13, 2026 — a gap of more than six months in which agencies could make no new awards.

2.4 IP structures deter entrepreneurs

University IP policies vary more than is generally appreciated, and the variation shapes outcomes. At most major US research universities, the institution owns patentable inventions produced with university resources, and inventors receive a share of licensing revenue — at Stanford, for example, typically one-third after costs, with the rest split between department and school.

The University of Waterloo takes the opposite approach. Since 1997, its Policy 73 has given ownership of intellectual property created in teaching and research to the people who create it, with limited exceptions such as sponsored contract research. Waterloo pairs that with dedicated support: a commercialization office (WatCo) and an incubator (Velocity), which by the university's count has helped launch more than 500 startups since 2008. The model has drawn international attention: in 2025, New Zealand announced it would develop a similar approach for its national research institutions.

The University of Toronto takes a middle path, an "inventor's choice" policy that lets inventors request personal ownership; inventors keep 75 percent of net revenue from inventor-owned IP and 60 percent from university-owned IP. The broader point is that IP structure is not a neutral administrative detail. It shapes whether researchers become entrepreneurs.

2.5 The regulatory knowledge gap — especially 505(b)(2)

The fifth cause is specific to regulated sectors — biopharma, medical devices, biologics — and is particularly acute in pharmaceutical reformulation. Most academic researchers, including those working directly on drug candidates, have no working knowledge of the regulatory pathways that determine whether their compound can reach the market. The FDA's 505(b)(2) pathway is the most important of these, and it is chronically misunderstood in the academy.

505(b)(2) permits an applicant to rely on investigations "not conducted by or for" the applicant and for which it does not have a right of reference — in practice, to build on the existing safety and efficacy data of an approved drug while introducing specific changes (new formulation, new indication, new route of administration, new combination). Of the 1,001 new drug applications the FDA approved between 2010 and 2020, **570 — 57 percent — went through 505(b)(2)**, most of them new formulations or new dosage forms. Development programs are typically far smaller and faster than for a new chemical entity. An industry analysis of 78 505(b)(2) products launched between 2013 and 2018, assuming roughly $15 million of R&D per product, estimated an average five-year sales-to-R&D ratio of about **26 times**.

The European equivalent, Article 10(3) of Directive 2001/83/EC (the "hybrid" application), permits reference to the preclinical and clinical data of a reference product when bioequivalence cannot be established alone. It functions similarly to 505(b)(2) and is under-used by academic spinouts for the same reason: the pathway is not taught in most PhD programs.

The consequence is that academic reformulation projects, which should be the cheapest and highest-ROI path in biopharma, frequently die because nobody in the lab group — or in the TTO — understands how to structure the regulatory package. This is a bottleneck that better tooling and training directly address.

2.6 Cultural attitudes are still ambivalent

Stuart and Ding, in a landmark 2006 *American Journal of Sociology* study of academic life scientists, found that "the orientation toward commercial science of individuals' colleagues and coauthors significantly influences scientists' hazards of transitioning to for-profit science." Mertonian norms — the notion that science should be communal, universal, disinterested, and organized around skepticism — have softened considerably since the Bayh-Dole Act of 1980, but they have not disappeared.

Johnson, in A *Fractured Profession* (2017), drew on interviews with 61 scientists at four US universities to document what he called intraprofessional conflict between "commercialists" and "traditionalists" over the proper relationship between research and commerce. In the life sciences, long-running concerns about industry influence on research have kept that tension alive.

Cultural attitudes are difficult to change directly, but they are responsive to peer example. When senior faculty at a department commercialize, the hazard rate for junior faculty rises. When a TTO produces visible successes, skepticism declines. The cultural barrier is real, but it is downstream of the structural ones.

2.7 The tooling gap

The seventh cause, and the one this paper will argue is most tractable, is operational. Academic research that reaches the point of potential commercialization is typically not "licensing-ready" in the form that a pharmaceutical acquirer, a strategic investor, or a Series A VC would expect. Specifically, it usually lacks:

- **A structured data room.** Diligence materials scattered across PI laptops, TTO files, and shared drives rather than organized in a virtual data room with clean version control.
- **A regulatory strategy document.** No written analysis of 505(b)(2) vs. NCE pathway, orphan or breakthrough designation potential, or comparable EMA routes.
- **A patent landscape map.** The original composition-of-matter patent, but no freedom-to-operate analysis, no blocking patent review, no family strategy.
- **A CMC and manufacturing plan.** Research-grade synthesis but no analysis of manufacturability at scale or API supply-chain risk.
- **Market sizing and competitive analysis.** Indications identified but no Target Product Profile, no epidemiology work, no payer analysis.
- **A risk-adjusted financial model.** Sometimes a high-level slide, rarely a defensible NPV built on trial-phase success probabilities.

- **A clinical development plan.** A plausible next study, rarely an end-to-end plan to an approvable filing.

The VDR market itself was worth approximately **$2.42 billion in 2024**, and Grand View Research projects it to reach $7.73 billion by 2030 at a 22.2 percent compound annual growth rate. Industry leaders — Datasite, Intralinks, DealRoom, Firmex, iDeals, Ansarada — are standard infrastructure for corporate M&A. They are not standard infrastructure for university research.

The operational gap is where AGCP has concentrated its own tooling investment. AGCP's development platform, now part of the Graticus software suite, combines data room functionality with regulatory intelligence for 505(b)(2), EMA hybrid and ANDA pathways; patent intelligence and prior-art tracking; vendor management; and exit-valuation planning. It was built first for our own licensing work, not as a commercial product. That is, in miniature, the story of most of the best operational tooling in this field: it emerges from operators who have crossed the Valley once and want to make the crossing faster the second time.

SECTION 03

The 2025–2026 US federal funding shock

The Valley of Death has been a chronic condition. In 2025 it became acute. The speed and breadth of the changes to US federal research funding since early 2025 have little modern precedent, and their consequences for global research translation will outlast the immediate policy fights.

3.1 NIH: the indirect cost fight

On February 7, 2025, NIH issued Notice NOT-OD-25-068, setting a flat **15 percent rate for indirect (facilities and administrative) costs** on its grants in place of the rates individually negotiated with each institution. For research-intensive universities, whose negotiated rates are typically far higher, the change would have cut NIH support by tens to hundreds of millions of dollars each.

The response was immediate. Twenty-two states, together with university and medical-school associations, sued in federal court in Massachusetts. The district court blocked the policy within days and made the block permanent on April 4, 2025. On January 5, 2026, the First Circuit unanimously affirmed, holding that the cap violated a long-standing appropriations rider protecting negotiated rates as well as HHS's own regulations. The government let its April 2026 deadline to seek Supreme Court review pass.

The legal fight over the cap is over. The policy signal is not. On August 21, 2025, the Supreme Court, by a 5–4 vote, allowed NIH to proceed with terminating about $783 million in grants linked to diversity, gender identity and related topics, while leaving in place the lower court's ruling against the guidance behind them. Across 2025, more than **3,800 NIH and NSF grants** were terminated or frozen, affecting roughly $3 billion in unspent funds.

For FY2026, the administration requested a cut of around 40 percent to NIH; Congress largely rejected it and held research funding roughly flat. The FY2027 request, released on April 3, 2026, again proposes cuts — about 13 percent for NIH and about 55 percent for NSF.

3.2 NSF: agency restructuring in real time

On April 18, 2025, NSF announced it was terminating grants no longer aligned with agency priorities, citing among others research on diversity, equity and inclusion and on misinformation. By late May, its public list showed **1,752 terminated grants worth about $1.4 billion**, with STEM education accounting for nearly half of the grants and about two-thirds of the dollars. On April 24, 2025, NSF Director Sethuraman Panchanathan resigned, amid reports of a planned 55 percent budget cut and large staff reductions.

Congress ultimately funded NSF at about $8.75 billion for FY2026, rejecting the proposed cut. But NSF's Graduate Research Fellowship Program selected about 1,000 fellows in 2025, roughly half its usual number, and the FY2027 request again proposes about $3.96 billion — a cut of nearly 55 percent.

3.3 Beyond NIH and NSF

Other agencies were affected too. The administration moved to dismantle USAID, long a major funder of global health research; in March 2025, Secretary of State Marco Rubio said that 83 percent of its programs would be cancelled, with the remainder absorbed into the State Department. The FY2027 request also proposes deep cuts to NASA science, DOE's Office of Science, EPA and NIST.

3.4 University-level consequences

The downstream effects on universities have been severe and concentrated:

- **Harvard**: In April 2025, the administration froze more than $2.2 billion in multi-year grants after Harvard rejected its demands, and Harvard sued. On September 3, 2025, Judge Allison Burroughs ruled the freeze unlawful, finding First Amendment and procedural violations, and most funding was subsequently restored. The government appealed; the First Circuit heard arguments on October 5, 2026, and a decision is pending.
- **Columbia**: In March 2025, about $400 million in grants and contracts was cancelled. In July 2025, Columbia agreed to pay $221 million to resolve federal investigations and restore its funding.
- **Johns Hopkins**: In March 2025, after losing more than $800 million in USAID funding, Hopkins eliminated more than 2,200 positions — 1,975 abroad and 247 in the US — the largest layoffs in its history.
- **Settlements**: Penn and Brown reached agreements in July 2025 (Brown's included $50 million for Rhode Island workforce programs over ten years), and Cornell and Northwestern later followed.

3.5 The private-sector response

The private sector has moved to fill parts of the gap. The Chan Zuckerberg Initiative's Biohub, which has given about $4 billion to basic science since 2016, said in November 2025 that it is on track to double that over the next decade, with an operating budget of about $1 billion a year. The Arc Institute, launched in December 2021 with more than $650 million in founding commitments,

fully funds Core Investigators for renewable eight-year terms in partnership with Stanford, UC Berkeley and UCSF. Other philanthropic and focused-research models are growing alongside them.

These are significant commitments. They are not, in aggregate, a replacement for federal funding: Congress appropriated more than $47 billion for NIH for FY2026 alone. The private-sector response is most valuable not as a substitute for federal funding but as an accelerant for the kinds of translational work that federal funding has historically underweighted — exactly the middle of the Valley of Death.

3.6 How this contraction differs from 2013 and 1995

Two prior US research funding contractions offer calibration. In 1995, proposed cuts to NIH gave way to a bipartisan effort that doubled its budget between 1998 and 2003. In 2013, sequestration cut NIH's budget by 5 percent, or $1.55 billion, and NIH estimated that it awarded about 640 fewer competitive research project grants as a result.

The 2025–26 contraction differs from both of its predecessors in kind, not degree. It involves the dismantling of an agency (USAID), topic-based mass terminations, an attempted indirect-cost cap that required court intervention, targeted university-by-university freezes, and negotiated settlements. By most accounts it is the most far-reaching restructuring of federal research funding in the post-war era.

SECTION 04

The international reshuffle

4.1 The US is no longer the only R&D superpower

According to the OECD's March 2026 release, global R&D spending reached about **$3.8 trillion in 2024**, and both the US and China crossed the $1 trillion mark. Measured at purchasing power parity, China's spending ($1.03 trillion) slightly exceeded that of the US ($1.01 trillion) for the first time; at market exchange rates, China's was about half the US level.

4.2 Europe opens the door

On May 5, 2025, European Commission President Ursula von der Leyen and French President Emmanuel Macron launched *Choose Europe for Science* at the Sorbonne. The initiative included:

- **€500 million package** for research and talent, 2025–2027.
- **New seven-year ERC "super grant"** to give leading researchers a longer-term perspective.
- **ERC relocation support doubled** from €1 million to €2 million.
- **A "Choose Europe" pilot** under the Marie Skłodowska-Curie Actions.
- **Freedom of scientific research** to be enshrined in EU law.

France added a further €100 million to attract researchers to French institutions.

Demand for Europe's deep-tech funding is also high: the European Innovation Council's October 2025 Accelerator cut-off drew 923 applications seeking nearly €7 billion.

The UK's June 2025 Spending Review set public R&D investment at £86 billion from 2026/27 to 2029/30, rising to £22.6 billion a year by the end of the period. Singapore's RIE2030 plan commits S$37 billion from April 2026, a 32 percent increase on RIE2025. Japan's ¥10 trillion university fund began supporting its first "University for International Research Excellence," Tohoku University, which was accredited in November 2024.

4.3 The brain drain is measurable

An opt-in *Nature* reader poll of more than 1,600 respondents in March 2025 found that 75 percent of US-based researchers were considering leaving the country, including 548 of 690 postgraduate researchers and 255 of 340 PhD students. *Nature* cautioned that the sample was not representative of US researchers as a whole.

The European Research Council recorded a clearer signal. Applications to its 2026 Starting Grant call reached a record **4,807 — a 22.4 percent increase** on the previous call, which had itself risen 13 percent. Applications from US-based researchers rose from 116 to 169, and women made up nearly 43 percent of applicants, the highest share since 2007.

4.4 Portugal and the AI² consolidation

Portugal's position in this reshuffle is worth specific note because it illustrates how mid-sized EU research systems are repositioning. Decree-Law No. 132/2025 of December 24, 2025 created **AI² (Agência para a Investigação e Inovação, E.P.E.)** by merging the Foundation for Science and Technology (FCT) with the National Innovation Agency (ANI). The new agency is to operate on a five-year multiannual budget, starting with the 2027–2031 cycle, intended to give research programs greater stability and predictability. The merger was contested: university rectors and parts of the scientific community warned that it could subordinate basic research to innovation goals.

For research-translational operators — AGCP included — Portugal's combination of EU regulatory access, moderate operating costs, an English-functional professional ecosystem, and a newly consolidated funding agency makes it an increasingly credible European base for translational work.

SECTION 05

What actually works: the global bridge-builders

The Valley of Death has been studied for twenty years. In that time, specific institutional models have crossed it more reliably than others. They differ in structure, geography, and sector focus, but they share a core logic: they replace the linear "grant → lab → TTO → lucky license" pipeline with a structured bridge staffed by people whose full-time job is crossing the Valley.

5.1 The Fraunhofer model (Germany, 1949)

The Fraunhofer-Gesellschaft — more than 30,000 staff and an annual budget of about €3.6 billion — is the closest thing the world has to a gold standard for applied research commercialization. The defining feature of the "Fraunhofer model" is that no more than one-third of its budget comes from base funding from the German federal and state governments, while at least two-thirds must be won through competitive contracts with industry and public-sector programs.

The effect is disciplinary. Every Fraunhofer institute is under constant pressure to produce research that someone outside the building will pay for; in 2025, industry revenue alone came to €966 million. Fraunhofer's best-known commercial success, the MP3 audio format developed at Fraunhofer IIS, generated licensing income for years until its key patents expired.

Various national programs have attempted to replicate the Fraunhofer model: the UK's Catapult Network, Singapore's A*STAR, Taiwan's ITRI, Canada's NRC-IRAP, Australia's Cooperative Research Centres. None has fully reproduced the combination of scale, funding discipline, and industry integration. The core insight — that institutes disciplined by contract funding produce different research than institutes protected from it — has been replicated imperfectly almost everywhere.

5.2 Creator-owned IP: the Waterloo model

Section 2.4 described the University of Waterloo's Policy 73, under which researchers own what they invent. What makes it work is the support around it: a commercialization office (WatCo) and the Velocity incubator, which by the university's count has helped launch more than 500 startups since 2008. In 2025, New Zealand's government announced it would develop a national IP policy for its research institutions modeled on Waterloo's approach.

5.3 Translational research institutes

The Broad Institute of MIT and Harvard, founded in 2004 with philanthropic support from Eli and Edythe Broad, became a template for privately supplemented translational research and has spun out companies including Editas Medicine, Beam Therapeutics, and Prime Medicine.

The Francis Crick Institute in London opened in 2016 as a partnership among the Medical Research Council, Cancer Research UK, the Wellcome Trust, UCL, Imperial College London, and King's College London, and is among the largest biomedical research centers in Europe.

The Arc Institute in Palo Alto, launched in December 2021 with more than $650 million in founding commitments — including from Stripe co-founder Patrick Collison — partners with Stanford, UC Berkeley, and UCSF and fully funds Core Investigators' labs for renewable eight-year terms, explicitly to free them from the grant cycle.

5.4 Venture builders

Flagship Pioneering, led by founder Noubar Afeyan, builds companies around its own scientific "what if?" questions rather than waiting for inventions to arrive. It has founded more than 100 companies, including Moderna, which it co-founded and incubated in 2010. In July 2024, Flagship raised $3.6 billion — $2.6 billion for Fund VIII plus $1 billion in side funds — bringing its assets under management to about $14 billion.

Third Rock Ventures, founded in 2007, took a similar build-it-yourself approach, with its partners initially running portfolio companies directly. Its companies include Agios, Blueprint Medicines, Foundation Medicine, and Global Blood Therapeutics, which Pfizer acquired in 2022.

Other venture builders, such as Deep Science Ventures in the UK, begin with the desired outcome rather than the underlying discovery, and accelerators such as SOSV's IndieBio take early-stage science teams through structured company-building.

5.5 University-affiliated venture funds

University-affiliated funds take a different route. Osage University Partners, founded in 2009, invests in academic spinouts through partnerships under which universities assign it co-investment rights in exchange for a share of the returns.

In the UK, Oxford Science Enterprises invests in Oxford spinouts alongside the university's technology transfer office, and Cambridge has a comparable ecosystem. The scale of the European opportunity is now measurable: the European Spinouts Report 2025, produced by Dealroom with Atlantic, Oxford Science Enterprises, Cambridge Innovation Capital, and others, values deep-tech and life-science spinouts from European universities at **$398 billion**, across more than 7,300 startups and over 167,000 jobs. Oxford, Cambridge, ETH Zurich, and EPFL lead for value creation.

Scale does not guarantee success. Publicly listed vehicles built to commercialize university IP across many institutions have struggled, often because their portfolios were concentrated and public-company costs were high relative to revenues. Academic spinouts at scale are hard even for funds that specialize in them.

5.6 What successful bridges have in common

Reading across these models, five attributes recur:

1. **Concentrated research excellence** combined with well-staffed technology transfer. Output tends to track the investment in translational staff.
2. **A co-investment vehicle** alongside the TTO, as at Oxford and Cambridge, so that promising spinouts can raise early capital quickly.
3. **Creator-friendly or inventor-favorable IP policy,** as at Waterloo and in the University of Toronto's inventor's-choice approach.
4. **A single point of contact** for industry, so that companies are not passed between separate licensing and industry-relations offices.
5. **Contract-research orientation.** The Fraunhofer rule — at least two-thirds of budget from competitive contracts — disciplines research toward translatable outputs.

A sixth attribute, implicit in all of the above but rarely stated: these institutions employ full-time operators whose job is crossing the Valley. They are not academics doing commercialization as a side project. They are former BD executives, former regulatory strategists, former investment bankers, former entrepreneurs — people who speak both languages and spend their days at the seam.

SECTION 06

The tooling and skills gap

The operational deficit described in Section 2.7 is the single most tractable constraint in the Valley of Death, and it is also the constraint that private operators — rather than federal policy or university reform — are best positioned to address. Better tooling and better training do not require Congress, do not require tenure reform, do not require a cultural shift in the academy. They require software and curriculum.

6.1 The virtual data room is now infrastructure

The virtual data room market was worth approximately **$2.42 billion in 2024**, and Grand View Research projects it to reach $7.73 billion by 2030 at a 22.2 percent compound annual growth rate. Leading vendors include SS&C Intralinks, Datasite, DealRoom, Firmex, iDeals, and Ansarada.

VDRs are standard infrastructure for corporate M&A, private equity, and biotech business development. They are *not* standard infrastructure for university research. Most university spinouts arrive at their first serious licensing conversation with diligence materials scattered across PI laptops, shared drives, and TTO file systems, which slows diligence and raises the buyer's perceived risk.

The tooling exists. The academic research ecosystem does not use it.

6.2 Regulatory intelligence and patent analytics

Beyond VDRs, three additional tooling layers are standard in industry and rare in academia. Regulatory intelligence platforms — Citeline (Informa/Norstella) and Clarivate Cortellis are the market leaders — provide structured data on clinical trials, drug approvals, regulatory pathways, and competitive landscapes. Patent intelligence platforms — PatSnap, Clarivate Derwent, LexisNexis PatentSight — provide family-level patent analysis, freedom-to-operate analytics, and portfolio valuation. TTO platforms — Wellspring, Inteum, Sophia — manage the disclosure-to-license pipeline itself.

Industry BD teams use all three. Most university TTOs, especially outside the top twenty by research spend, use none systematically. The result is that academic licensing conversations frequently run on incomplete or out-of-date information on both sides — the inventor does not know the regulatory landscape or the competitive IP, and the acquirer has to build that analysis from scratch, raising perceived risk and lowering offered valuation.

6.3 How AGCP's development platform approaches the problem

AGCP's development platform — built first for our own licensing work and now part of the Graticus software suite — integrates these functions into a single workflow. Its modules include:

- **Data room** with role-based permissions, audit trails, and document management.
- **Regulatory intelligence** covering FDA 505(b)(2), EMA hybrid, ANDA, 505(b)(1), and formulations-to-regulatory integration, with document generation, timeline planning, and authority interaction logs.
- **Patent intelligence** with invention disclosure forms, prior art tracking, PCT preparation, strategy branch modeling, and US non-provisional workflow support.
- **Vendor and purchase management,** including CRO and CDMO tracking.
- **Exit valuation planning,** with risk-adjusted NPV modeling and comparable-transaction analysis.
- **Development briefs** generated from a compound, linking formulation, regulatory, and IP analysis into a single plan.

The platform was built because we needed it. In conversation after conversation with prospective academic partners, the same gap appears: the science is strong, the IP is real, and the operational layer needed to make the assets licensable does not exist. Whether that layer is built on our tools or on anyone else's is less important than the broader point: it is now a prerequisite for translational work, not an accessory to it.

6.4 The skills gap: what works in training

NIH's I-Corps program, adapted from Steve Blank's Lean LaunchPad methodology and the Business Model Canvas, takes NIH-funded researchers through an intensive program of structured customer discovery, which participants use to test whether — and for whom — their technology solves a real problem.

The deeper evidence base for commercial training in professional education comes from simulation-based learning research. Sitzmann's 2011 *Personnel Psychology* meta-analysis covered 65 studies with 6,476 participants and reported that trainees taught with computer-based simulation games scored **20 percent higher on post-training self-efficacy**, **11 percent higher on declarative knowledge**, **14 percent higher on procedural knowledge**, and **9 percent higher on retention** than comparison groups. Cook and colleagues, publishing in JAMA in 2011, reviewed 609 studies with 35,226 participants in health professions education and found effect sizes of 1.20 for

knowledge, 1.09 to 1.18 for skills, 0.79 to 0.81 for behaviors, and 0.50 for direct patient effects. The JAMA authors concluded that "technology-enhanced simulation training in health professions education is consistently associated with large effects."

The debriefing layer matters as much as the simulation itself. Fanning and Gaba, reviewing the field in *Simulation in Healthcare* in 2007, described debriefing as "facilitated or guided reflection in the cycle of experiential learning" and noted that feedback, including debriefing, had been identified as the most important feature of simulation-based medical education. Savoldelli and colleagues, publishing in *Anesthesiology* in 2006, were direct: "exposure to a simulated crisis without constructive debriefing by instructors offers little benefit to trainees." The underlying learning model is Kolb's experiential learning cycle (1984): concrete experience, reflective observation, abstract conceptualization, active experimentation.

6.5 How PharmaSim approaches the problem

PharmaSim, the pharmaceutical training simulation suite AGCP offers through Graticus, implements a Teach → Simulate → Debrief architecture informed by this literature. It currently includes 13 simulations, each about four hours long and structured as ten modules, covering the commercial and regulatory decisions at the heart of pharmaceutical development — among them pipeline prioritization, regulatory pathway selection, licensing negotiation, and clinical trial design trade-offs. Each is built around structured teaching content, a sequence of consequential decisions, and a guided debrief.

The target learner population is not undergraduates or MBAs. It is the postdoctoral researcher, the junior TTO officer, the PI considering a spinout, the graduate student deciding whether to pursue an I-Corps track — the specific population that the Valley of Death data says is least equipped to translate their science, and that the meta-analytic simulation literature says responds most strongly to experiential learning interventions.

As with the development platform, the question of vendor is less important than the question of whether the skills layer exists at all. At present, in most academic research environments, it does not. Fixing that is a necessary condition — not a sufficient one, but a necessary one — for crossing the Valley at scale.

SECTION 07

The commercial opportunity

7.1 Sizing the dormant IP

The aggregate commercial opportunity represented by unlicensed university IP is difficult to size precisely, but the order of magnitude is knowable. AUTM's 2025 data show 28,278 invention disclosures against 10,277 licenses and options executed — so in any given year, new disclosures far outnumber the deals signed. The AUTM–BIO analysis estimates that university and nonprofit inventions contributed up to $1.9 trillion to US gross industrial output from 1996 to 2020 — roughly $75 billion a year from the subset that does reach the market.

Even conservative estimates of the commercial value forgone from the large majority of disclosures that never become products run into the hundreds of billions of dollars over a decade. This is the raw material of the opportunity.

7.2 When research commercializes, the returns are extraordinary

Individual success stories indicate the upper bound of the distribution. Genentech, co-founded in 1976 by UCSF's Herbert Boyer, was later acquired in full by Roche. Moderna, co-founded by Flagship in 2010 on academic research, and BioNTech, founded in Mainz in 2008, became two of the most valuable biotech companies in the world during the COVID-19 pandemic.

Individual biopharma licenses have produced comparable outcomes at the university level. In 2005, Gilead and Royalty Pharma paid Emory University **$525 million** for its emtricitabine royalty interest — at the time described by Emory as the largest such sale. In 2007, Royalty Pharma paid New York University **$650 million** for its Remicade royalty, and later that year paid Northwestern University **$700 million** for part of its royalty interest in Lyrica.

7.3 The reformulation-specific opportunity

Within biopharma, the reformulation playbook — applying nanoemulsion, liposomal, nanoparticle, solid-dispersion, or similar approaches to existing molecules via the 505(b)(2) or EMA hybrid pathway — has produced a specific subclass of exits that are both achievable and attractive.

Consider four:

- **Abraxane** (nab-paclitaxel): FDA approved in January 2005; Celgene acquired its developer, Abraxis BioScience, in 2010 for about **$2.9 billion**. Abraxane reformulated paclitaxel to eliminate the Cremophor solvent that had constrained the original drug.

- **Doxil** (liposomal doxorubicin): the first FDA-approved nanomedicine, approved in November 1995 and invented by Yechezkel Barenholz and Alberto Gabizon. The first FDA-approved generic did not arrive until February 2013 — a testament to how hard complex nano-formulations are to copy.
- **EXPAREL** (Pacira's liposomal bupivacaine): FDA approved in October 2011; **2023 net product sales of $538.1 million**; more than 14 million patients treated by early 2024.
- **Alkermes** (acquired Elan Drug Technologies in 2011): a long-acting injectable portfolio including Vivitrol and Aristada, and the NanoCrystal technology behind Johnson & Johnson's Invega Sustenna — examples of the commercial longevity of well-designed reformulation IP.

Market research firms size the nanomedicine and drug-delivery market anywhere from tens to hundreds of billions of dollars, depending on definitions. The underlying substrate — poorly soluble compounds sitting in academic laboratories and industry archives — is effectively inexhaustible at current rates of reformulation.

7.4 Why 2025–2026 is uniquely attractive

Four conditions are aligned for the first time in a generation:

1. **US federal funding pullback** is forcing universities to seek commercialization partners and non-federal revenue at unprecedented scale.
2. **Biotech capital and dealmaking** are recovering from the 2022–2023 trough, and large pharmaceutical companies continue to source much of their innovation externally.
3. **AI-assisted drug discovery** is maturing from hype toward utility. Isomorphic Labs, spun out of Google DeepMind, raised $600 million in March 2025, holds partnerships with Eli Lilly and Novartis worth up to nearly $3 billion in milestones, and is preparing to bring its first AI-designed drugs into clinical trials.
4. **505(b)(2) is now the majority pathway,** accounting for 57 percent of FDA new drug application approvals from 2010 to 2020 — a structural shift that rewards precisely the reformulation skills that AGCP and similar operators specialize in.

Deloitte's latest analysis of the 20 largest biopharma companies shows the average R&D cost per asset still rising, to $2.67 billion in 2025 — which strengthens the case for sourcing de-risked external assets. The demand side is ready. The supply side — academic IP that is licensing-ready — is the bottleneck.

SECTION 08

Policy and institutional recommendations

The Valley of Death will not be closed by any single intervention. It will be narrowed by a combination of policy changes, institutional reforms, and private-sector operational investments. This section offers specific recommendations organized by audience.

8.1 For policymakers

Preserve Bayh-Dole in its current form. The 1980 Bayh-Dole Act has been widely credited — *The Economist* once called it possibly the most inspired American legislation of the preceding half-century — and the cumulative economic impact documented by AUTM and BIO supports that view. NIST's December 2023 draft guidance proposing price as a factor in march-in decisions has not been finalized; a 2026 GAO report found that NIST had no timeline for finalizing it. Agencies have received about a dozen march-in requests since 1980 and have declined every one. Introducing price-based march-in would chill the public-private partnerships that Bayh-Dole enables.

Fund the translational middle directly. The six-month SBIR/STTR lapse from October 2025 to April 2026 sent exactly the wrong signal at exactly the wrong moment. Now that the programs are reauthorized through 2031, Congress should sustain funding for SBIR/STTR, ARPA-H, and NSF's Regional Innovation Engines, and should consider expanding proof-of-concept funds modeled on programs such as the University of Michigan's Coulter partnership.

Incentivize TTO modernization. Federal capacity-building grants for technology transfer offices should be expanded, and their criteria should reward the attributes associated with strong TTO performance: single-point-of-contact models, co-investment vehicles, and operational tooling.

8.2 For university administrators

Reform tenure to reward commercialization. Surveys find that most universities still do not count patents or commercialization in tenure and promotion decisions, and Texas A&M's 2006 "sixth factor" remains a model few have followed. Commercialization and other knowledge-transfer activity should count toward promotion by default rather than by exception.

Consider creator-owned IP models. Waterloo's Policy 73 is unusual in North America, but its entrepreneurial record — and New Zealand's decision to emulate it — is difficult to ignore. The University of Toronto's inventor's-choice policy offers a middle path. Institution-owned IP is not a neutral default; it is a policy choice with downstream effects.

Build or contract for the operational layer. The tooling gap — VDRs, regulatory intelligence, patent analytics — is the cheapest structural problem to fix. Universities that lack the budget for enterprise licenses should consider consortium arrangements or external partnerships. Universities that have the budget should deploy the tools. The cost is modest relative to the licensing value at stake.

Invest in commercial skills training. I-Corps should be the floor, not the ceiling. Universities should build or license simulation-based commercial training programs for PhD students, postdocs, and junior faculty. The meta-analytic evidence for simulation-based learning is robust. The implementation cost is low. The return — in terms of disclosures translated, spinouts formed, and licensing revenue generated — will be meaningful within a five-year window.

8.3 For researchers

Ask what happens next before you publish. A disclosure filed after publication is worth less than a disclosure filed before. This is not a complicated calculus, and most TTO offices will support researchers who raise it early. The cultural habit of publishing first and thinking about IP later is a specifically pre-Bayh-Dole habit that Bayh-Dole eliminated the reason for.

Learn the regulatory pathway your work implicates. If you work on small-molecule drug candidates, learn 505(b)(2) and the EMA hybrid route. If you work on biologics, learn the BPCIA. If you work on devices, learn 510(k) and PMA. The knowledge is freely available, and the lack of it at the PI level is a common reason academic drug candidates are undervalued in licensing conversations.

Consider a commercialization-track program or fellowship. Programs such as I-Corps improve outcomes directly, and they also improve outcomes indirectly by building the network that makes later commercialization easier.

Partner with operators, not just capital. A $10 million Series A check without operational help is worth less than a $3 million check from a partner who brings regulatory strategy, BD relationships, and tooling. The best translational investors know this. The best academic entrepreneurs learn it, usually the hard way, after a round or two. Learning it earlier saves time and dilution.

8.4 For entrepreneurs and investors

Build tooling, not just term sheets. The fund that writes the $10 million check is one of a hundred. The operator who shows up with a VDR template, a 505(b)(2) regulatory memo, a patent landscape map, and a CMC plan is one of five. Universities have never needed capital more than they do now, and they have never been more willing to work with partners who bring operational infrastructure alongside money.

Target the reformulation opportunity. Up to 90 percent of molecules in discovery pipelines are poorly water-soluble. The 505(b)(2) pathway accounted for 57 percent of FDA new drug application approvals from 2010 to 2020, and one industry analysis estimated an average five-year return of about 26 times R&D spend for 505(b)(2) launches. The tooling (nanoemulsion, lipid nanoparticle, nanocrystal, solid dispersion) is mature. The substrate (academic drug candidates with established mechanism but poor bioavailability) is abundant. This is an unusually favorable configuration for a commercial opportunity.

Plan for the fifteen-year window. The 2025–2026 US funding contraction, the European and Singaporean expansions, the brain drain signals from *Nature* and the ERC, the AI-drug-discovery maturation, and the structural shift toward 505(b)(2) all point toward a fifteen-year window during which the institutional landscape of global research commercialization will be redrawn. Operators who build infrastructure during this window will own the next generation of translational outcomes. Those who wait for stability will find that the stable state already belongs to someone else.

CLOSING

Conclusion: the fifteen-year window

I have argued four things in this paper. First, that the Valley of Death between academic research and commercial product is a structural feature of the global research system, measurable in the AUTM funnel and the biopharma attrition curve, and persistent across funding cycles and institutional types. Second, that the 2025–2026 US federal funding shock is qualitatively different from its 2013 and 1995 predecessors and will reshape global research flows for years. Third, that the most tractable levers — the ones not dependent on legislation or cultural change — are operational tooling and commercial skills, both of which have mature markets and evidence bases that the academy has largely not adopted. Fourth, that the reformulation opportunity specifically — driven by the high share of pipeline molecules that are poorly soluble and by the 505(b)(2) pathway that now accounts for most US NDA approvals — is an unusually favorable configuration for operators who can combine science, regulatory strategy, and business development.

The Valley is not closing on its own. But for the first time in a generation, the conditions for narrowing it — the capital, the institutional dislocation, the regulatory pathway, the tooling technology, and the global talent reallocation — are simultaneously present. The fifteen-year window that opens in this decade will determine whose institutions, whose tools, and whose trained researchers define the next era of translational science.

The most important thing universities lose when research dies on campus is not royalty revenue. It is patients who never get a treatment that should have existed, farmers who never get a drought-resistant variety that should have existed, communities who never get a water-purification technology that should have existed. The economic case for commercialization is strong. The human case is stronger.

AGCP was built — and our development platform and PharmaSim were developed — on the premise that the Valley is solvable in specific, concrete, operational ways. The approach does not require waiting for Congress or reforming tenure committees or convincing anyone that commercialization is virtuous. It requires building the tools, teaching the skills, and partnering with researchers whose work deserves to leave the lab.

The work deserves to leave the lab. That is the whole argument. Everything in this paper is in service of making it more likely to actually happen.

NOTES

Sources and methodology

This paper draws on primary and authoritative secondary sources compiled in April 2026 and re-verified in November 2026. Peer-reviewed sources are listed with full citations; figures from reports, official releases, and news reporting are attributed to the original publisher wherever possible.

Drug development cost estimates span from about $172.7 million (Sertkaya 2024, mean out-of-pocket cost) to $2.87 billion (DiMasi 2016, including post-approval R&D), depending on methodology. The Amgen and Bayer reproducibility figures come from studies that did not identify the papers involved. Poor-solubility estimates (roughly 70 to 90 percent of candidates) are industry estimates cited in reviews rather than a single primary dataset. The *Nature* brain-drain poll was opt-in and not representative. AUTM data are self-reported. The 505(b)(2) return estimate assumes a fixed R&D cost per product. Where these figures appear, I have used them directionally and, where estimates disagree, presented the range.

Any errors, omissions, or misinterpretations are mine alone.

About the author

Lawrence Fine is CEO and Co-Founder of AGCP Farmacêuticos, a pharmaceutical nanotechnology company based in Lisbon, and leads Graticus, its software and simulation brand. He spent 17 years at Microsoft in a range of leadership roles, has led turnarounds and growth strategies as an independent advisor, and has served on a number of boards. He is the author of five books on leadership and holds a PhD in Engineering from Stanford University and an MBA from Emory University.

About Graticus

Graticus, part of AGCP Farmacêuticos, builds scenario-based simulations that help people develop real-world judgment, along with a development platform for early-stage pharmaceutical work. Its focus is on practical skills and measurable results.

graticus.com · hello@graticus.com

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