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REVIEW ARTICLE

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De-risking transformative microscopy technologies for broad adoption

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Abstract

The past 20 years have seen a paradigm-shifting explosion of new optical microscopy technologies aimed at uncovering fundamental biological insights. Yet only a small portion 'cross the finish line' into wide adoption by the life science community. We contend that this is not primarily due to a lack of technical prowess or utility. Rather, many risks can conspire to derail the adoption of potentially disruptive technologies. One way to address these challenges is to de-risk paradigm-shifting inventions within open-access technology incubators. Here we detail the framework needed to shepherd innovative microscopy techniques through the often-treacherous adoption landscape to enable transformative scientific output.

KEYWORDS

microscopy development, microscopy dissemination, technology validation, technology de-risking

1 | INTRODUCTION

It is widely accepted that microscopy provides a broad and versatile toolset for life scientists. Yet, this statement belies its full value. A recent survey of biology publications indicated that up to 70% of data are imaging-based[1] firmly cementing microscopy as an absolutely essential tool in biology. While the proliferation of new imaging technologies is fed by enormous advances from academia and industry, it is not uncommon for the journey from inception to commercialisation to last a decade, if at all.[2] Indeed, the severity of the barriers is commonly, and ironically, proportional to the disruptive potential of the newly developed microscopy technology. Furthermore, many scientifically impactful technologies may not be suitable for commercialisation in the first place. This underscores the importance for alternative pathways to reach a wider scientific community.

Figure 1 summarises possible pathways to bring a microscope from inception to adoption. Commercialisation has long been the primary and often most effective route. However, it is fraught with risks and challenges both before and after market entry (Figure 2).[2] It is increasingly clear that marketability alone cannot be the sole criterion for dissemination. Thus, alternative and effective dissemination routes are increasingly being utilised. One pathway that has recently received increasing popularity is the instrument replication model.[3] Yet it requires long-term specialised expertise and resources that may not be readily available in many institutions. To complete the landscape, open-access platforms[2,4] provide a means for researchers to use technologies who may be otherwise hesitant or unable to purchase or duplicate them. Nevertheless, the high investment cost and geographical scarcity of such platforms can also limit their reach. Regardless, each pathway converges ultimately on a single common goal for success: the microscope is used to generate scientific output.

Most instruments, unfortunately, do not achieve this ultimate success easily. This propensity for failure lies in

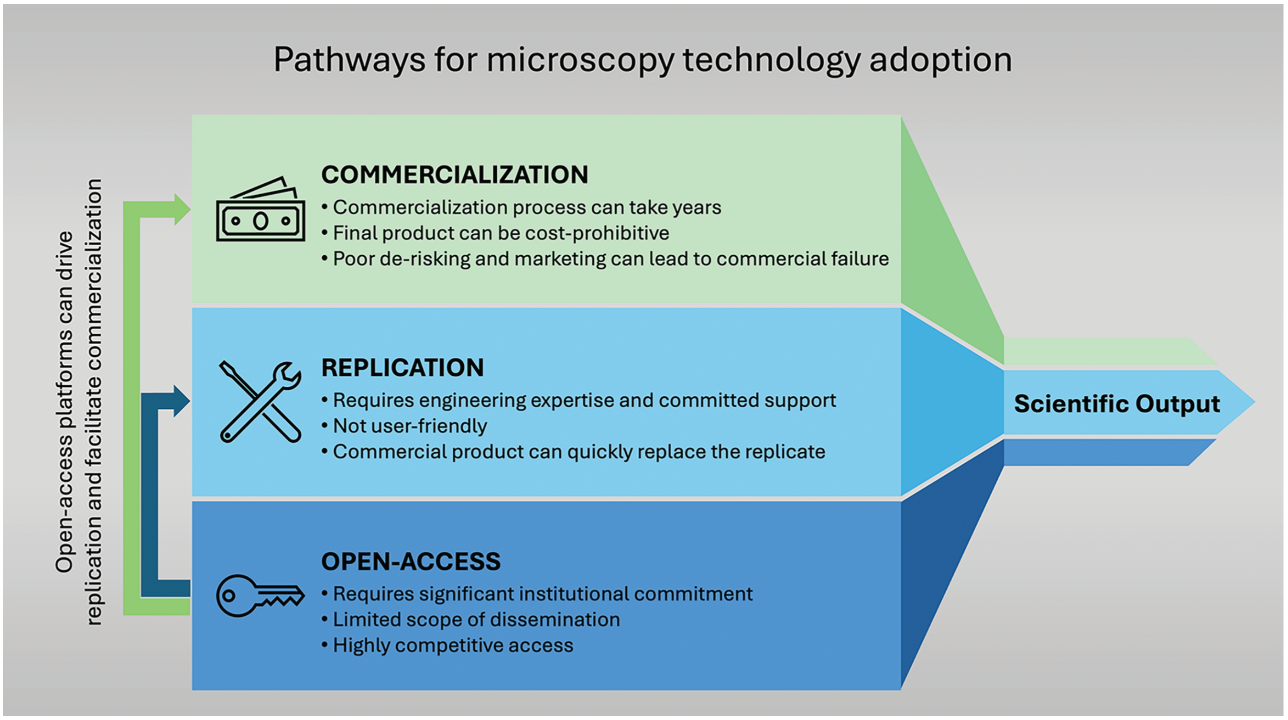

FIGURE 1 'Buy it, clone it, or try it': commercialisation, replication and open-access platforms constitute three common pathways for microscopy technology adoption. Each pathway has its own pitfalls or limitations, but they can also cater to different needs. Having a potentially transformative technology in a fully supported, open-access microscopy incubator can, in turn, catalyse both instrument replication and subsequent commercialisation.

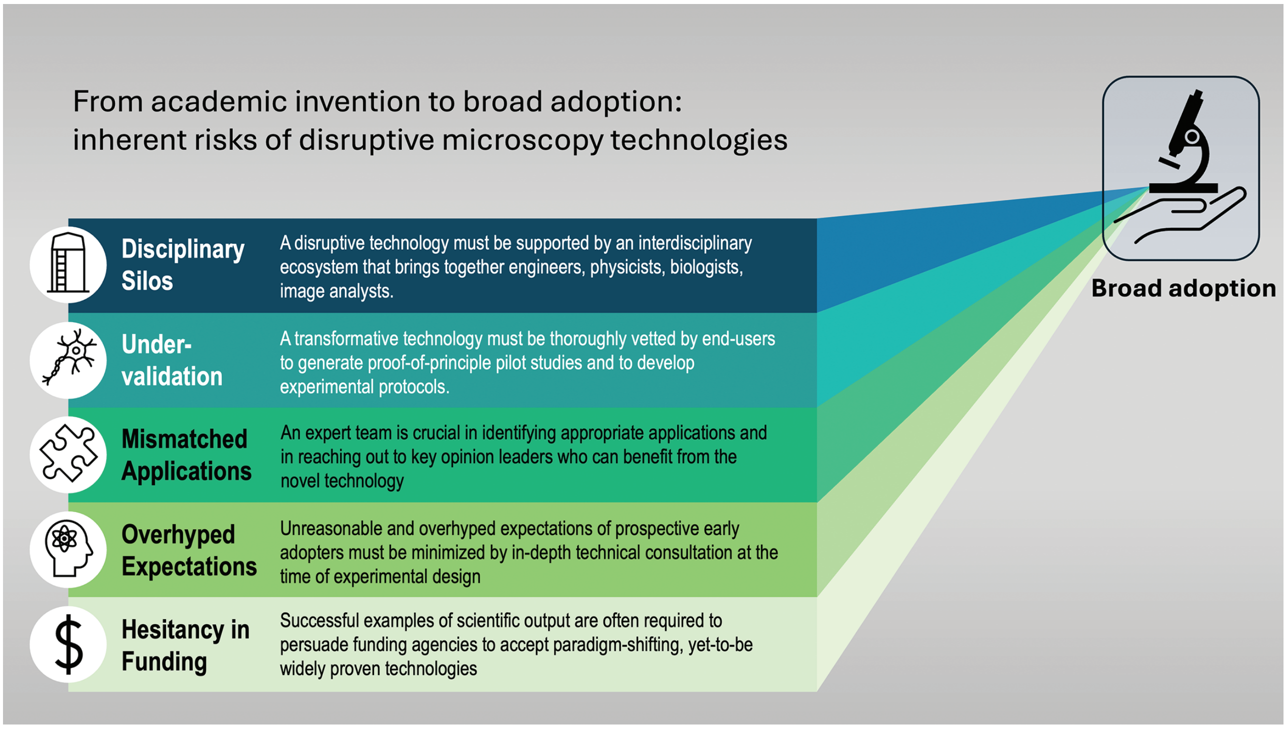

FIGURE 2 The path to broad adoption for disruptive imaging technologies is fraught with risks that must be carefully mitigated. Due to their paradigm-breaking nature, disruptive technologies face numerous and perilous risks that can lead to an insurmountable chasm in the adoption process. These threats, however, can be neutralised through a multi-pronged de-risking strategy.

the fact that most technologies are deprived of a comprehensive 'de-risking' strategy, which can provide a litany of essential benefits. We have previously discussed the operational details underpinning the successful creation of open-access ecosystems[4] as a path towards technology dissemination. Here, we share the strategic vision of the Advanced Imaging Center (AIC) at HHMI Janelia Research Campus as a unique way to de-risk microscopy uptake. In it, we outline the threats faced by imaging technologies, and chart a roadmap for success.

2 | CHALLENGES FACED BY NASCENT TECHNOLOGIES

Stakeholders that support imaging technology development face a persistent, debilitating challenge: How to best ensure a new innovation will generate scientific output. Put simply, a new technology cannot be transformative if it cannot transform research. Unfortunately, several strategic and systemic barriers can lead this effort astray.

2.1 | Undervalidation

Any imaging technology must contend with fundamental trade-offs to balance image quality, spatiotemporal resolution, field of view and specimen health.[5,6] Compounded with this, many new imaging methods demand unique but often poorly validated and inaccessible sample preparation techniques. Additionally, they often place crushing burdens regarding data handling,[7] including data processing algorithms that face their own unique set of challenges to adoption.

Unfortunately, institutions and funders alike also exert enormous pressure on microscope developers to quickly generate publications that showcase a new microscope in as positive a light as possible. These pressures place an overwhelming incentive to avoid discussions of limitations, or even a comprehensive technical validation that are crucial for long-term adoption. Indeed, such analyses are often wholly absent from the literature. This leaves potential users of a new technology ill-informed when performing their own experiments; a poor understanding of the constraints and requirements of a new microscopy technique will nearly always guarantee experimental failure and eventual technology abandonment.

2.2 | Academic siloing

Microscope developers generally have primary expertise and focus in physics and engineering, and new advances are typically first reported in journals or conferences that cater exclusively to these fields. This academic siloing tends to make novel, transformative imaging technique invisible to the very end-users who stand to benefit most from them. Taken together, expertise compartmentalisation and institutional/funder pressures drive down developer motivation to conduct wide-ranging and resource-intensive explorations to address diverse biological questions. This can result in technologies languishing as merely proof-of-principle demonstrations, rather than being paired to novel applications to transform biological inquiry.

2.3 | Lack and mismatch of applications

Optimally pairing a new microscope to the right applications requires both (i) an insight into the underlying technology and (ii) an ability to translate descriptive biological semantics into quantitative image-based readouts[8] so that the biological applications can fully take advantage of the instrument capabilities. As a result, the siloing of expertise can make this task challenging. Technology developers may excel in the first arena but lack sufficient biological expertise to accomplish the second. Collaborations between technology developers and biologists can certainly bridge this gap but can often be ad hoc and both time- and resource-intensive.[2] At worst, developers may prioritise collaborations with biologists as a means to supply specimens to test their nascent technology, with little regard to the possible biological insights such testing may bring. As a result, a comprehensive understanding of the types of questions that a microscope is best suited to address is often difficult to discern for developers and users alike. In the end, failing to find suitable applications for a new technique can diminish initial excitement, and risk underutilization.

2.4 | Overhyped expectations

Even if cross-disciplinary technical validation and innovative application of a new imaging technology is successful, further risks abound. Arguably the most insidious hazard is hype. Whether through aggressive marketing by commercial manufacturers, or zealous promotion by developers themselves, a promising technology can easily turn into an overpromised technology. Unfortunately, it is not uncommon for early adopters to find themselves disappointed by initial uninformative image data, or other difficulties in navigating a new microscope. The inevitable 'bursting of the bubble' from repeated underdeliveries or, worse yet, failures can cause initial enthusiasm to overcorrect to cynicism about developers' claims, again leading to abandonment.

2.5 | Funding uncertainty

Taken together, the aforementioned risks can conspire to form the greatest peril: uncertainty. There is an often-dichotomous reception from end-users to new technologies. Risk-averse users will tend to wait until there is enough evidence and general recognition, slowing the pace of technology uptake. Conversely, early adopters, who are also often key opinion leaders, may project unrealistic expectations of what the technology can deliver, leading to disillusionment that subsequently threatens adoption. This widespread uncertainty leaves funders in an understandable, but paralytic 'wait and see' stance that fuels a vicious cycle. On the one hand, funding is critical for generating novel biological insights across a range of applications. Yet funders may be reluctant to support a nascent technology until a critical mass of such successes are already achieved. This impasse can quickly calcify into inaction and failure of adoption.

3 | CHARTING A ROADMAP FOR SUCCESS

Of the various paths to adoption, none are mutually exclusive. However, open access platforms can uniquely reinforce the other routes (Figure 1). For researchers wishing to replicate an instrument, open access platforms offer a low-risk environment for testing and evaluation before committing resources to build their own. Likewise, open access environments provide a powerful 'proving ground' for technologies on a path to commercialisation. They not only provide valuable validation to inform design improvements, but also deliver the critical technology-application matching task to manage user expectations before it becomes too late, or too costly, to remedy. Additionally, their experience can inform other commercialisation pitfalls such as large data management, unique sample preparation and mounting workflows, as well as limitation of current design.

We and others have advocated for open-access imaging platforms,[4,9] not just as centres of technological excellence, but as critical knowledge distribution hubs that share unbiased experience and feedback on new imaging technologies. But simply placing a fleet of precommercial imaging systems into an open access environment is woefully insufficient. To catalyse such tools into wide adoption, a purpose-built ecosystem with the right resources and, most importantly, a clear vision must exist (Figure 3).

3.1 | Multidisciplinary ecosystem and personnel support

It is a common misconception to assume that precommercial imaging technologies simply require appropriate optical expertise coupled with design/manufacturing resources to be effective. A full complement of supporting technologies and application scientists must form an interdependent, multidisciplinary network comprised of biologists, engineers/physicists, probe developers, data scientists and even ancillary support staff to guide nascent technologies towards wide adoption.[4,10]

Personnel must also be unencumbered by institutional or interdepartmental barriers that slow communication and impede collaboration. But beyond resources, technical acumen, and administrative efficiency, imaging centre staff must be willing to shepherd a user's project, with deep commitment and nimbleness, from inception through completion. The ability to quickly grasp initially unfamiliar biological phenomena and 'translate' a descriptive hypothesis into a quantitative, interpretable experimental design can form the backbone for a successful imaging project.

Beyond inception, however, it is essential for imaging centre staff to deftly monitor and steer a user project continuously throughout its execution. Whether through giving incisive advice on sample preparation and imaging parameters, critical feedback on data quality, or guidance on data analysis and results interpretation, each team member's role is interconnected and complementary to promote project success. This deep commitment to comprehensive and agile project management can distinguish a truly effective imaging platform from merely a well-resourced one.

3.2 | User and developer engagement

The power of nascent technologies may not always be immediately apparent. Even for well-established researchers, the disruptive nature of a new technology can paradoxically trigger a lack of trust rather than ignite excitement in its capabilities. This often leads to instrument underutilisation in many technology incubators, an occurrence captured by the common aphorism 'if you build it, they won't come'.[4] To counteract this often-difficult conundrum, it is vital to directly engage with as many potential users as possible. This global level of engagement is laborious, time-consuming and inevitable. It necessitates a concerted effort to inform and inspire researchers across the globe and research disciplines alike, as to the untapped potential of a new technology.

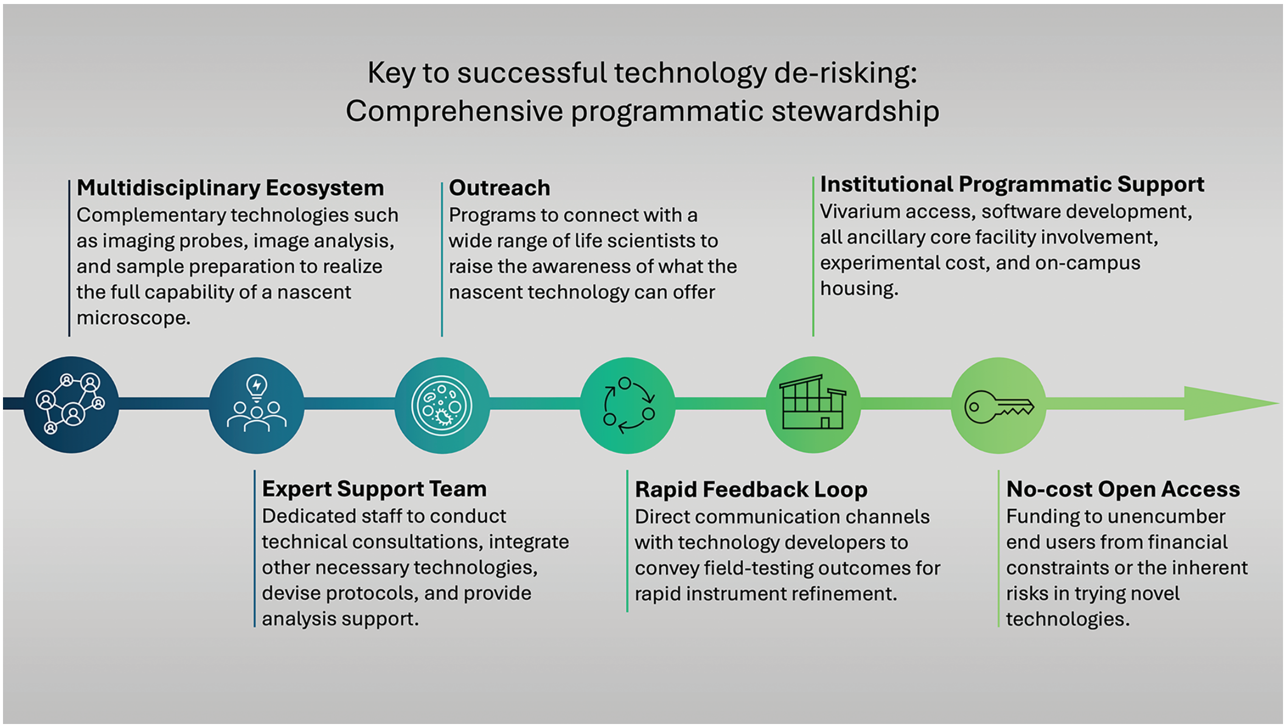

FIGURE 3 **An effective de-risking process for microscopy technologies entails more than validation**. To successfully pave the way for a disruptive microscopy technology to broad adoption, a comprehensive, well-supported, multi-pronged stewardship that extends far beyond validation of the technology is required.

Also commonly overlooked is the fact that scientific diversity is critical to thoroughly map the technological capabilities and limitations as part of any de-risking process. A microscopy technology incubator therefore will be most effective when its access policies are inclusive of the wider biological community, irrespective of research field, geography or laboratory largesse. Additionally, such equitable policy further prevents unnecessary alienation of biologists with equally appropriate but underexplored topics.

Strategically established at the interface between end users and tool builders, such technology incubators are natural liaisons between them. Through well-honed intuition and experience, imaging platform scientists can identify promising but largely unproven technology developments that are primed for adoption. Reciprocally, the team can also effectively translate user needs into concrete technological improvements in system performance, adaptability and ease-of-use.

3.3 | Institutional support and vision

Taken together, effective technology de-risking requires both (i) an internal ecosystem to support user needs and experimental success, as well as (ii) cultivation of a global external ecosystem to ensure that technologies are thoroughly tested on a variety of problems. Doing so requires a significant level of planning, investment and ultimately commitment from institutional leaders.

From an internal standpoint, an institution must be willing to remove academic and administrative boundaries. Open access imaging platforms cannot effectively operate as interlab or interdepartmental collaborations, but rather as a single, integrated and autonomous entity. There must also be a willingness to support facile procurement of reagents and equipment to enable rapid and flexible responses to user needs.

Concomitantly, a broader externally facing approach must envelop these internal administrative strategies. An imaging platform can only be truly responsive when its host institution recognises the imperative of proactively welcoming the worldwide scientific community within its walls. Chief among these is the ability to support streamlined mechanisms to host visiting scientists, with on-site housing, food service and easy visitor access to labs, facilities and other research spaces.

But most fundamentally, an institution must embrace the very spirit of Open Science. Many transformative precommercial imaging technologies may represent a significant revenue opportunity. But prioritising profit over adoption negates the very essence of this discussion. Therefore, a no-cost model singularly becomes the most equitable and effective means to this end. Providing free access to precommercial imaging technology by no means diminishes the prospects of commercialisation or replication as routes to adoption – in fact, as we have already discussed, it can be vital to enhancing them. A no-cost open access model removes barriers to access, freeing a technology to be broadly tested, validated, improved upon, leaving its strengths to be leveraged for enabling scientific output. More than any other consideration, this represents the single most valuable return on investment.

4 | DISCUSSION

The integration of advanced microscopy in life sciences crossed an inflection point when biologists no longer feel confined by a complete reliance on commercial instruments. What was previously perceived by many as an insurmountable hurdle of adopting a newly developed, potentially transformative microscopy technology has been gradually supplanted by the confidence and desire to be at the forefront of imaging science. While commercialisation remains the most effective dissemination pathway, it is no longer the only approach. It is now complemented by other creative solutions such as instrument replication via open sharing of blueprints, as well as the proliferation of open-access imaging centres with the provision of precommercial instruments as their *raison d'être*. These alternative avenues are crucial for funders who seek to ensure that the technologies developed with their support can be maximally utilised.

However, a microscopy technology is considered disruptive for a reason. Not only must it be capable of transforming the type of data that can be acquired, but it should also fundamentally shift the paradigm of how experiments can be designed and therefore how biological questions can be formulated. Precisely because of its propensity to steer researchers into previously uncharted territory, the path to its broad adoption is rife with risks that can hinder its adoption. In fact, the promise of a novel technology is predicated on pairing its validated, unique, capabilities with the appropriate applications. Unmitigated hype and overenthusiasm do not propel a technology. In reality, they constitute pernicious risks as they are unforgiving of underdelivery and failures. In this article, we summarise these risks and provide a solution based on the demonstrated success of the AIC at the HHMI Janelia Research Campus.

While targeted investment can quickly build the necessary infrastructure, the underlying motivation of creating such a technology incubation centre cannot be based on the short-term infusion of funds. Striking a multifaceted balance requires a unique ecosystem capable of bringing all the necessary ingredients together. For such a multidisciplinary, open-access incubator to thrive in the long run, the institutional ethos must be firmly anchored in the central tenet of technology-sharing. Protectionist ownership, where a centralised microscopy platform exclusively possesses the transformative technologies, is antithetical to the spirit of dissemination. A microscopy incubator platform should set its sight on engendering equitable access through transparent policy, engaging in proactive global outreach and creating training opportunities for prospective users, unencumbered by geographical constraints.

It is also important to note that, due to inevitable limitations on space, budget and personnel faced at every institution, each equipment in the instrument portfolio incurs a cost – the opportunity cost of not being able to offer full stewardship for an additional emerging technology on the horizon. It is therefore strategically expedient to find a suitable off-ramp to transition de-risked technology to a secondary site, especially if commercialisation is not an immediate option. This cascading dissemination model is beneficial for several reasons: (i) it frees up the resources so that the incubator centre can begin the de-risking process for the next transformative technology, (ii) the sufficiently de-risked instrument can be replicated and adapted to local needs and operations, and (iii) it rapidly expands the impact of the technology through this distributed approach.

While the AIC strategy is by no means the only formula for success, it dispels the conventional notion that a technology will be readily adopted once its performance has been benchmarked. Technology validation per se is necessary, but it is insufficient to carry a technology, as transformative as it may be, across the finish line. To fully de-risk a paradigm-shifting technology, the axiom of 'programmatic stewardship' (Figure 3) must be firmly established as the cornerstone of any strategy.

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