International Journal of Project Management 38 (2020) 256–266

Contents lists available at ScienceDirect

International Journal of Project Management

journal homepage: www.elsevier.com/locate/ijproman

Resource interdependence and project termination: An analysis in the biopharmaceutical industry

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ARTICLE INFO

Keywords:
Project portfolio management
Uncertainty
Project termination
Drug discovery and development
Interdependencies

ABSTRACT

Firms typically manage project portfolios with specific characteristics, including lengthy and high-risk projects with many similarities in human and technological resources and whose sequence and movement through the pipeline create longitudinal interdependencies. Interdependencies increase the complexity of project portfolios and create constraints in decision-making. This paper focuses on resource interdependencies and aims deepen our understanding of the extent to which resource interdependencies affect project termination. We study a sample of 417 new biotechnology-based drug discovery and development projects initiated by 25 biopharmaceutical SMEs. To test the hypotheses, we employ survival analysis and model terminations as a conditional probability and a corresponding hazard function. Our results show that for drug development projects, only certain types of interdependencies have a significant effect.

1. Introduction

R&D projects involve a high degree of uncertainty due in part to the unpredictability of immediate returns. The termination rate for such projects has been estimated to range from 40 to 75% (Shih, Zhang, & Aronov, 2018; Stevens and Burley, 2003). The significant financial and non-financial losses that can be associated with R&D projects warrant a study on the reasons for project termination.

Most analyses of project termination focus on individual projects in isolation (Biedenbach and Müller, 2012; Unger, Kock, Gemünden, and Jonas, 2012). They have shown that the determining factors for R&D project termination relate to parameters such as high-risk investments (Conti, 2014; Pammolli, Magazzini, and Riccaboni, 2011), lack of exploitable knowledge created (Bonabeau, Bodick, & Armstrong, 2008), the firm's inability to leverage its exploration and exploitation experience for R&D projects (Hoang and Rothaermel, 2010), the collaboration structure (e.g., Mishra, Chandrasekaran, and MacCormack, 2015; Pisano, 1997), the firm's position in an interfirm knowledge network (Dong and Yang, 2016), and more generally, the project's characteristics, with the causes of termination varying by project type (Pinto and Mantel, 1990).

Yet R&D firms typically manage multiple projects. Unlike traditional projects in the construction field, for example, the value of an R&D project does not stem solely from its cash flow. An R&D project is undertaken primarily in order to generate knowledge that may be useful for ongoing or future projects. Hence, pharmaceutical and biopharmaceutical companies have adopted pipeline thinking, whereby they conduct a sufficient number of R&D projects in a portfolio at different stages of development (Gassmann and Reepmeyer, 2005). These projects tend to have specific characteristics. They may be lengthy and/or high-risk projects that draw on overlapping human and technological resources, such that they are in competition with each other (Girotra, Terwiesch, and Ulrich, 2007). Consequently, the sequence and movement of the projects through the pipeline create longitudinal interdependencies (Blau, Pekny, Varma, and Bunch, 2004)–. These interdependencies increase the complexity of project portfolios and constrain decision making (Ghasemzadeh and Archer, 2000; Killen and Kjaer, 2012). Hence, any change in a project decision is likely to affect other projects (Bathallath, Smedberg, and Kjellin, 2016; Berggren, 2019; Teller, Unger, Kock, and Gemünden, 2012). In the case of biopharmaceutical project development, Khanna, Guler, and Nerkar (2018)p. 2441) note that "the increase in interdependencies within and across research areas brings about the need to understand their implications for managerial decisions. Ignoring these interdependencies could lead to an incomplete or incorrect understanding of the research process."

This paper therefore focuses on resource interdependencies within project portfolios. The aim is to deepen our understanding of the extent to which resource interdependencies affect project termination. We

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https://doi.org/10.1016/j.ijproman.2020.06.001
Received 20 January 2019; Received in revised form 21 February 2020; Accepted 4 June 2020

examine a sample of 417 new biotechnology-based drug discovery and development projects initiated by 25 biopharmaceutical SMEs. To test our hypotheses, we perform a survival analysis using Cox's maximum likelihood proportional hazard model (Cox, 1972) to estimate the termination hazard for individual projects.

The biopharmaceutical industry provides an instructive setting to examine the impact of project interdependencies on the project termination rate. Due to the complexity of R&D projects, interdependencies in this context are particularly important (Khanna et al., 2018). In this industry, all the different development stages are governed by regulations, and all biopharmaceutical firms must follow the same development stages (Girotra et al., 2007). This allows identifying projects at the same stage across different firms. New drug development is a sequential process that entails three major stages: discovery (preclinical development), development (clinical trials), and launch (commercialization) (e.g., Lim, Garnsey, and Gregory, 2006). In the discovery or preclinical development stage, promising biologically derived products are investigated and tested for safety and effectiveness in treating diseases. By the end of this stage, approximately half of all new projects are abandoned due to infeasibility (Lowman, Trott, Hoecht, and Sellam, 2012; Pisano, 1997). Next comes the clinical testing stage, which includes three types of trial: Phase I, Phase II, and Phase III. Phase I trials are conducted in relatively small numbers of healthy volunteers. In Phase II, the drug is tested for safety and effectiveness in treating a disease in actual patients. In Phase III, larger samples, typically comprising several thousand patients, participate in trials to assess the drug's effectiveness and safety relative to standard treatments.

This study complements the current literature on portfolio project management in two ways. First, it focuses on the project termination decision. The majority of studies address the consequences of this decision, for portfolio performance (Lechler and Thomas, 2015; Unger et al., 2012), for careers (Balachandra, Brockhoff, and Pearson, 1996), for learning (Shepherd, Patzelt, Williams, and Warnecke, 2014), for project team resilience (Moenkemeyer, Hoegl, and Weiss, 2012), or for the project managers who terminate the projects (De, 2001; Todt, Weiss, and Hoegl, 2018). In addition, most studies that investigate the project termination decision adopt the perspective that managers base their decisions on best estimations of the expected value of the project. However, interdependencies between projects increase the complexity of these decisions (Khanna et al., 2018). This study adds to the literature by investigating the role of project portfolio complexity through an historical analysis of resource interdependencies. In line with Thompson's (1967) typology, we distinguish three types of interdependence: 1) pooled, when projects are in a common technological field (Gear and Cowie, 1980; Verma and Sinha, 2002); 2) sequential, when the technical knowledge gained from one project provides usable information to another (Blau et al., 2004; Gear and Cowie, 1980); and 3) reciprocal, when different projects run concurrently compete for the same resources (Blau et al., 2004; Teller et al., 2012).

2. Termination and project interdependencies

A project termination is viewed as a "failure" even though the decision not to pursue an ineffective project should be thought of as a "success" (Boehm, 2001; Peck, Lendrem, Grant, Lendrem, and Isaacs, 2015). The decision to end a project is generally considered to be one of the most important and difficult decisions that managers must make (Peck et al., 2015; Unger et al., 2012). Two themes appear relevant to understanding the project termination decision.

The first theme is the omnipresence of human behavior: decisions are made by people, and people are subject to powerful cognitive biases (Staw, 1981). In addition, the effectiveness of these decisions depends on the speed of their application (Peck et al., 2015). However, a hasty decision may meet with resistance due to the serious consequences. For instance, the project team may believe that their personal success and career are intrinsically tied to the project (Peck et al., 2015). There may also be considerable responsibility associated with the termination decision (Statman and Sepe, 1989). Alternatively, the project may be forced to continue under pressure of institutional policies (Guler, 2007) or due to organizational disfunction (Lechler and Thomas, 2015).

The second theme is that decision-making reflects a rational tendency. In this sense, projects are terminated when the results supporting their continuity are lower in value than the termination value (Statman and Sepe, 1989). This implies that information is available to managers in order to estimate future results. Project portfolio management, or the decision-making processes for a set of projects (Killen, Hunt, & Kleinschmidt, 2007), proposes normative frameworks and techniques for project evaluation, selection prioritization, and termination (Cooper, Edgett, and Kleinschmidt, 2001; Unger et al., 2012). The decision-making processes also depend on the characteristics of the portfolios, and more particularly, on their degree of complexity. For instance, Buonansegna, Salomo, Maier, and Li-Ying (2014) stress that unmanageable portfolio complexity may explain the managerial rationale for terminating projects. These authors define project portfolio complexity in terms of the geographical distribution of projects, the complex environment of stakeholders, and the number of partners involved. Project portfolio complexity can also stem from project interdependencies (Verma and Sinha, 2002; Cooper et al., 2001; Teller et al., 2012).

Interdependencies exist when the value of an activity (or project) depends on how other activities (or other projects) are carried out (e.g., Levinthal, 1997). Interdependence theory distinguishes between three different patterns of interdependence that represent varying intensities or degrees of linkage between projects (Thompson, 1967). Some projects are based on pooled technical resources that are used independently and that make independent contributions. This kind of interdependence has been called *pooled interdependence* (Thomson, 1967). In this case, the project portfolio is considered technologically coherent because it combines technologies that share a common knowledge base and rely upon common scientific principles or have similar heuristics of research (Breschi, Lissoni, and Malerba, 2003). *Longitudinal interdependencies* (Kock and Gemünden, 2019; Thompson, 1967) are theoretically defined as a unidirectional exchange pattern where each unit's inputs are the outputs from another unit (Victor and Blackburn, 1987). Consideration of longitudinal interdependencies led to emphasis on the learning potential of projects (Berggren, 2019). In other words, the learning contents of a technology project may be used in subsequent projects (Brady and Davies, 2004). Longitudinal interdependencies result in knowledge interdependencies (Teller et al., 2012). For example, technical success or failure affects a subsequent project's probability of technical success (or failure) (Blau et al., 2004). In this way, pooled and longitudinal interdependencies produce a learning curve effect that is both unintended (in terms of spillover) and intended (in terms of local learning) (Breschi et al., 2003). The third type of interdependence is *reciprocal interdependence*, which is considered the highest degree of interdependence. It occurs when projects depend on the same resources (particularly human resources) for their execution (Engwall and Jerbrant, 2003). Reciprocal interdependence usually stems from efforts to cut the total portfolio cost (Schmidt, 1993). This needs coordination by mutual adjustment, and it requires resource allocation planning and scheduling (Galbraith, 1973; Thompson, 1967). Nevertheless, as Engwall and Jerbrant (2003) point out, managers face challenges in the planning, scheduling, and allocating of resources among simultaneous projects. Reciprocal interdependencies therefore play a role in decision making at the portfolio level. For instance, Engwall and Jerbrant (2003) show that when projects lag behind schedule, it may be impossible to use the appropriate resources as originally envisaged. Consequently, instead of upfront planning, the resources are allocated among ongoing projects ex-post. Interdependencies affect the number of information cues that managers must process as well as the changes in how these cues interrelate over time (Ethiraj, Ramasubbu, and Krishnan, 2012).

Project portfolios for pharmaceutical drug discovery exemplify the three kinds of interdependencies in "a hierarchical complex system that

is composed of a succession of interrelated subsystems with their own subsystem" (Khanna et al., 2018p. 2448).

2.1. Pooled technology interdependencies and termination of r&d projects

Some firms rely heavily on building their internal technological strength, including the extent of technological knowledge they need to gain competitive advantage and ensure their survival (Hoang and Rothaermel, 2010). Pooling technologies across projects helps develop fungible assets. Fungibility is considered a firm-level capability that allows firms to re-apply their existing capabilities to other areas, thereby cutting investment costs (Vassolo, Anand, and Folta, 2004). If several investments draw from a common pool of technologies, the firm may be able to take advantage of economies of scope and learning spillovers (Verma and Sinha, 2004). For instance, firms could take general technological knowledge that is generated in one research area and transfer it efficiently to other projects (Cockburn and Henderson, 2001) to create new market niches. Consequently, when a firm invests in multiple projects, the fungibility of shared technologies among several projects means that investments can be partially redeployed across the projects, thereby raising their value and hence the value of the portfolio (Vassolo et al., 2004). In other words, a diverse portfolio in terms of the number of different technologies used moves a firm "away from its experience curve, reducing the overall aggregated probability of success and potential value" (Tiggemann, Dworaczyk, and Sabel, 1998, p. 817).

Thus, the more projects that use common technologies, the more the firm can develop its internal exploration and exploitation capabilities (Verma and Sinha, 2004). This is especially true in the case of the life sciences sector, where the distinction between product and process innovation is not clear cut. In the biotechnology sector, process development is an integral aspect of product development. The pharmaceutical development process usually involves new and untried technologies that are developed iteratively and are therefore continually revised as more is learned (Lim et al., 2006). Developing projects based on existing technological knowledge helps the development team clearly articulate the R&D steps, work methodically through the steps, and solve problems when and as they occur (Verma and Sinha, 2004). In this way, companies can leverage their technological knowledge to develop new projects and reach new markets. For example, the Kirin Corporation, which previously operated in the beer market, reused their expertise in large-scale fermentation technology to move into anticancer drug discovery.[1] Merck, Sandoz, and Takeda used their microbiological capabilities to develop new drugs such as Ivermectin, an effective treatment for tropical filariasis (Drews, 2000).

In sum, through the development and re-application of technological knowledge and expertise, companies can improve their innovative capacity (e.g., Bolívar-Ramos, García-Morales, and García-Sánchez, 2012). Furthermore, complementarities resulting from interdependencies decrease the probability of stopping a project (Khanna et al., 2018). Consequently, pooling technologies among projects may reduce the probability of project termination. This leads to the following hypothesis:

Hypothesis 1. Pooled technology interdependence among projects is negatively associated with R&D project termination.

2.2. Longitudinal interdependencies and r&d project termination

The expected probability of technological success is a critical variable that reflects the feasibility of a project. Thus, when technological problems cannot be resolved or a new problem appears, the probability of a subsequent project's success declines (Guan, Liu, and Peng, 2002) in the presence of longitudinal interdependencies. For instance, drug development projects may use different technologies according to the maturity of "the underlying scientific fields, the relevant scientific theory, and the availability of process engineering heuristics" (Pisano, 1996, p. 1101). To illustrate, Soxhlet solvent extraction and infusion are traditional techniques used to extract constituents (Qaraghuli, Alzahrani, Niwasabutra, Obeid, and Ferro, 2017). In a radical departure from this method, nanobiotechnology techniques have been found to improve the therapeutic index and provide solutions to drug delivery problems for new classes of biotech drugs (Dinda and Pattnaik, 2013). These products require a learning-by-doing process for the efficient development of process technology (Pisano, 1996). Learning by doing "typically refers to the automatic process by which the firm becomes more practiced, and, hence, more efficient at doing what it is already doing" (Cohen and Levinthal, 1989, p. 570). During the development process, technological solutions are identified and tested, and the best ones are retained (Danzon, Nicholson, and Pereira, 2005). Learning from in-practice technology use is therefore a *non imitable* key to success (Lowman et al., 2012). Consequently, the probability of technological success depends on the development sequence, such that the technological success (or failure) of a drug candidate affects the probability of technological success (or failure) for an as-yet-untested trailing drug candidate. Thus, if the first drug in the sequence of drugs targeted for a disease fails, the probability of technological success for all succeeding drugs decreases at a higher rate than if the first drug in the sequence succeeds (Blau et al., 2004). In a case study, Aaltonen (2010) also suggests that although managers can formally decide to terminate projects, drug development terminations are often decided by external stakeholders, for technological reasons. Project termination reduces the company's learning capacity for the technology and increases technological uncertainty, which in turn diminishes the potential benefits of intensifying future investments in this technological direction.

Accordingly, in the same way that success breeds success, termination breeds termination. Therefore, technological termination interdependence can explain the choice to terminate some projects. Given that technological termination interdependence is a longitudinal type of interdependence, we propose the following hypothesis.

Hypothesis 2. Longitudinal interdependence between projects is positively associated with project termination.

2.3. Reciprocal interdependencies and r&d project termination

Lack of resources constitutes a barrier to both innovation (Gann and Salter, 2000) and project performance (Verma and Sinha, 2002). This can be the result of reciprocal resource interdependencies. In the case of multiproject management, the "resource allocation syndrome" is a predominant issue that usually stems from many other, more profound organizational problems in the multiproject setting (Engwall and Jerbrant, 2003). According to Girotra et al. (2007), the resource scarcity problem during a developmental stage can result from poor estimation of success probabilities at earlier stages. For example, introducing too many projects into a portfolio can increase competition for resources and hinder project development (McDonough and Spital, 2003). This is known as the "canary cage" problem (Clark and Wheelwright, 1992), whereby a company continues to add canaries (projects) to the cage (the portfolio) without considering those already inside. Reciprocal interdependencies then lead to challenges. In the drug industry, during the clinical trial stage (Phases II and III), and irrespective of disease or medical indication, all compounds can draw from the same pool of resources (Blau et al., 2004; Ho & Gibaldi, 2004). However, as the drug moves down the pipeline from Phase II to Phase III, the financial costs and resources required for testing increase dramatically (DiMasi, 2001, 2003; Pisano, 1997). These resource capacities are generally costly to scale in the short term, being mostly hired professionals or fixed assets. Moreover, they take time to set up, particularly for clinical Phase III, which requires numerous resources (DiMasi and Grabowski, 2007). Consequently, firms prepare by setting up clinical phase capacities well in advance of obtaining results, and in light of the expected probability of

[1] https://www.kirinholdings.co.jp/english/company/rd/.

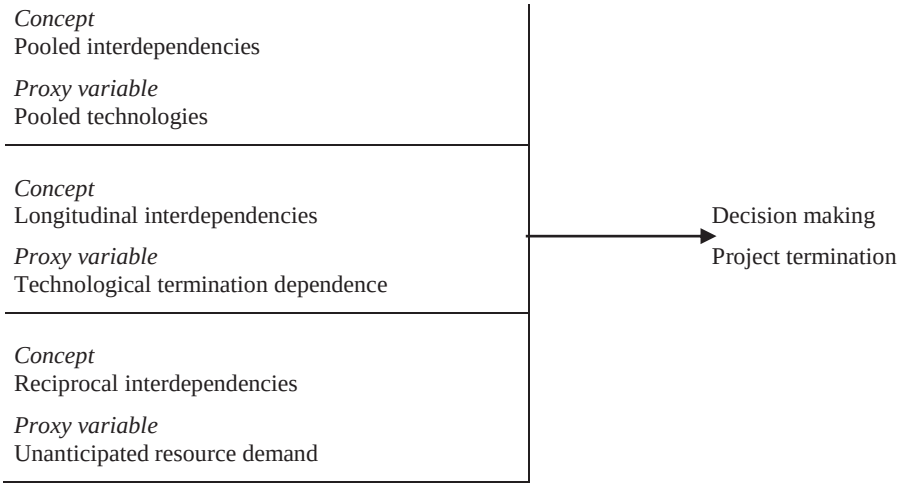

Fig. 1. Conceptual framework.

success based on previous phases (Girotra, Terwiesch, and Ulrich, 2004). Freezing these resources makes them unavailable to other projects.

Hence, due to resource interdependencies, terminations can occur even when the earlier success rate in the firm's pipeline is higher than expected. Accordingly, Pinto and Prescott (1990) consider project termination as the release of a project's resources and the reassignment of project team members to other duties. Thus, "[a] failure leads to the freeing up of resources shared by the failed and other projects. These freed-up resources can be redirected to other projects, which may then be brought to the market sooner than they would be if there was no failure" (Girotra et al., 2007, p 1453). In sum, since an enterprise typically has a given pool of resources, when there is high reciprocal interdependence of resources among projects, an unanticipated demand for resources increases the likelihood of project termination. In this way, unanticipated resource demand can affect the project termination decision. We therefore propose the following hypothesis.

Hypothesis 3. Resource reciprocal interdependence is negatively associated with project termination.

We integrated the three above-presented hypotheses to develop a theoretical framework linking pooled, longitudinal, and reciprocal interdependence with project termination in a multiproject R&D environment (Fig. 1).

3. Methodology

3.1. The drug development project context

Biopharmaceutical firms usually manage a portfolio of drug development projects. The portfolio may be more or less diversified in terms of therapeutic indications, technologies and resources, mechanisms of action, and development phases. Technological advances have revolutionized how new drugs are discovered. Synergies between genomics, robotics, miniaturization, screening methods, and information technologies have fueled the discovery of new candidate drugs. Consequently, the number of potential drugs entering the pipeline is growing, along with the size of firms' R&D project portfolios. In a drug development pipeline, new products in various development phases form repeating sequences of similar projects involving very similar activities that must be repeated (Jekunen, 2014). Portfolio management is particularly suitable for the pharmaceutical industry, because "the cost of new drug development is critically dependent on the proportion of drugs that fail in clinical testing" (DiMasi, 2001, p. 297).

3.2. Data

The database for the survival analysis included all R&D projects implemented from 1990 to 2012 by 25 small- and medium-sized U.S. firms operating in biotechnology and drug discovery (a total of 451 projects). The majority of biopharmaceutical companies are small- or medium-sized, and 72% of U.S. biopharmaceutical firms have fewer than 50 employees (OECD statistics, 2014).

First, we randomly selected 185 public U.S. biopharmaceutical firms from the total number of firms (1896) with fewer than 500 employees that are listed in the ReCap database. We then selected companies that were involved in drug discovery, for which most R&D project information was available in the ReCap database, and for which financial data was available in Compustat (25 companies). The ReCap database is the most comprehensive publicly available data source documenting clinical trial processes in the global biotechnology industry (see Schilling, 2009, for details). ReCap tracks, for every biopharmaceutical firm, the therapeutic products that have undergone the clinical trial process. Each record of product trials contains information on the medical indications (e.g., hepatitis C, ulcerative colitis), technologies used (e.g., carbohydrates, peptides, synthetics and semi-synthetics, phototherapy, drug delivery, monoclonal antibodies), therapeutic areas (e.g., cancer, cardiovascular, endocrinological, metabolic), mechanisms of action (e.g., topoisomerases, telomerase RNA), the partners involved, time when the product enters each stage of the clinical trial process, name of the company that originated the project, origin of the compound, name and description of the product, and date of project start and termination. This information largely covers the development history of the company's drug development projects, or its project portfolio. However, not all projects in the ReCap database have a project start or termination date. We therefore obtained the missing project dates from other databases, such as BioScan, firm websites, and a fine-grained analysis of scientific articles. Of the 451 projects, 234 (51.32%) were conducted alone by a biopharmaceutical firm and 222 (49%) were conducted in cooperation with one or more pharmaceutical firms. Of the same 451 projects, 379 (84%) were initiated by the biopharmaceutical firms and 77 (17%) were in-licensed. A total of 34 (7.54%) new biotechnology drugs reached the market, of which five were subsequently withdrawn. After eliminating these 34 projects (being successfully completed, they were removed from the list of projects at risk of being terminated), we retained a sample of 417 R&D projects. Of these, 209 were terminated in the 1990–2012 period under observation.

Table 1 presents the sample description. Fig. 2 shows an example of an R&D project portfolio in the sample. It includes six projects, the first three of which were initiated in 1996 and 2004 and were based on the same group of technologies (Drug Delivery – Oral, Peptides). (Fig. 3.)

Table 1
Drug development process: sample description.

	Basic research	IND review → Pre-clinical	Phase I	Phase II	NDA review → Phase III	Approval → Market	Total
Compound discovery and screening		Animal testing for safety and metabolism	Safety in small sample of healthy volunteers	Safety and efficacy in sample of patients	Safety and efficacy in large sample of patients		
Number of ongoing projects	9	17	62	102	18	29	237
Number of terminated projects	4	4	52	124	25	5	214
% of terminated projects	31%	19%	46%	60%	58%		
Total number of projects	13	21	114	226	43	34	451

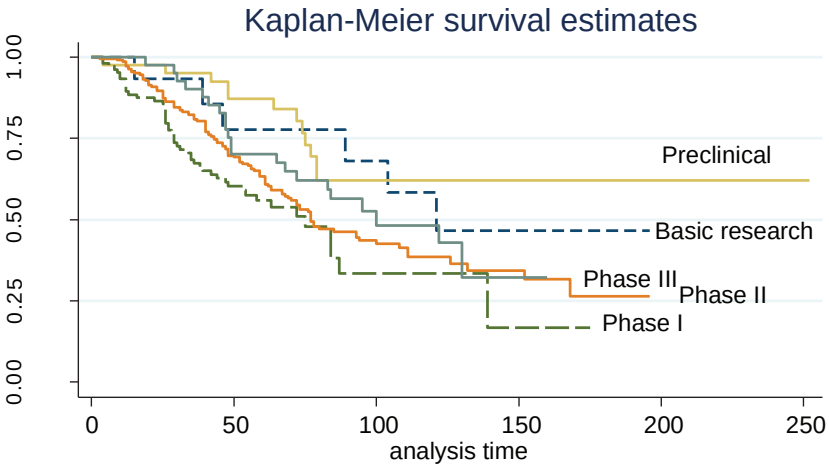

Fig. 2. Plots of survivor functions for drug development phases.

3.3. Measurement

3.3.1. Dependent variable: project termination

The dependent variable, *project termination*, is the hazard rate for project termination. The hazard rate incorporates information on whether the event occurred (*event* is a dichotomous variable that takes the value of 1 if the project is terminated and 0 if not) and project duration (variable *time*) (Allison, 1984). The variable *time* is proxied by the number of months from project initiation to project termination. During the observed period, 209 of the 417 projects were terminated—the event of focus—while the others were right-censored because they were outstanding at the end of the observation period.

3.3.2. Independent variables

Pooled technology interdependence is measured as the percentage of firm projects at time *t* that used the same technology combination *i* as the target project. Each project is based on one technology or a combination of several technologies. In the former case, we counted the number of projects using the same technology at *t*, and in the latter case we counted the number of projects that used the combination of technologies at *t*.

$$Pooled\ technology\ interdependence_{it} = \frac{Number\ of\ projects\ using\ technology\ i_t}{Total\ number\ of\ projects_t}$$

Two projects using the same technologies that are developed at the same time by the same company will therefore have an identical technological interdependence project indicator.

Longitudinal interdependence is proxied by *Project technological termination interdependence*, measured as the number of previous suspended and failed projects that used the same technology (or combination of technologies) *i* as the target project (number of project in *t-1*) divided by the number of projects using technology *i* at *t*.

$$Longitudinal\ interdependence_{it} = \frac{Number\ of\ previous\ \text{suspended and failed}\ projects\ using\ technology\ i_{t-1}}{Number\ of\ projects\ using\ technology\ i_t}$$

Reciprocal resource interdependence is proxied by the *unanticipated demand* for target phase resources, captured by the difference between the recent success rate and the expected previous phase success rate (in Phase I and the effect in Phase II, in Phase II and the effect in Phase III). Compounds that are successful in Phase I (Phase II) trials constitute the demand for Phase II (Phase III) resources. Following Girotra et al. (2007), to compute the Phase I (Phase II) success rate, we divided the number of successful trials (across all indications) in Phase I (Phase II) by the total number of Phase I (Phase II) trials (sum of the number of successes and failures across all indications) over the time period for the target firm. We computed the recent success rate by calculating the number of successes and failures in the 365-day period preceding the day of failure announcement. Because the firm establishes the capacity of Phase II (Phase III) resources on the basis of the expected Phase I (Phase II) probability of success, the actual demand for Phase III resources at any point in time is a function of the actual conduct of recent Phase I (Phase II) trials (Girotra et al., 2007). The unanticipated demand is therefore the difference between the recent success rate and the long-run success rate.

$$Unanticipated\ demand\ for\ Phase\ i\ resource = Recent\ success\ rate_{(Phase\ i)} - Long\text{-}run\ success\ rate_{(Phase\ i)}$$
$$= \frac{No.\ of\ successes_{\ i,t\in[-365,0]}}{No.\ of\ successes_{i,t\in[-365,0]} + No.\ of\ failures_{\ i,t\in[-365,0]}} - \frac{No.\ of\ successes_{i,\forall t}}{No.\ of\ successes_{i\forall t} + No.\ of\ failures_{\ i,\forall t}}$$

With Phase *i* = Phase I, Phase II

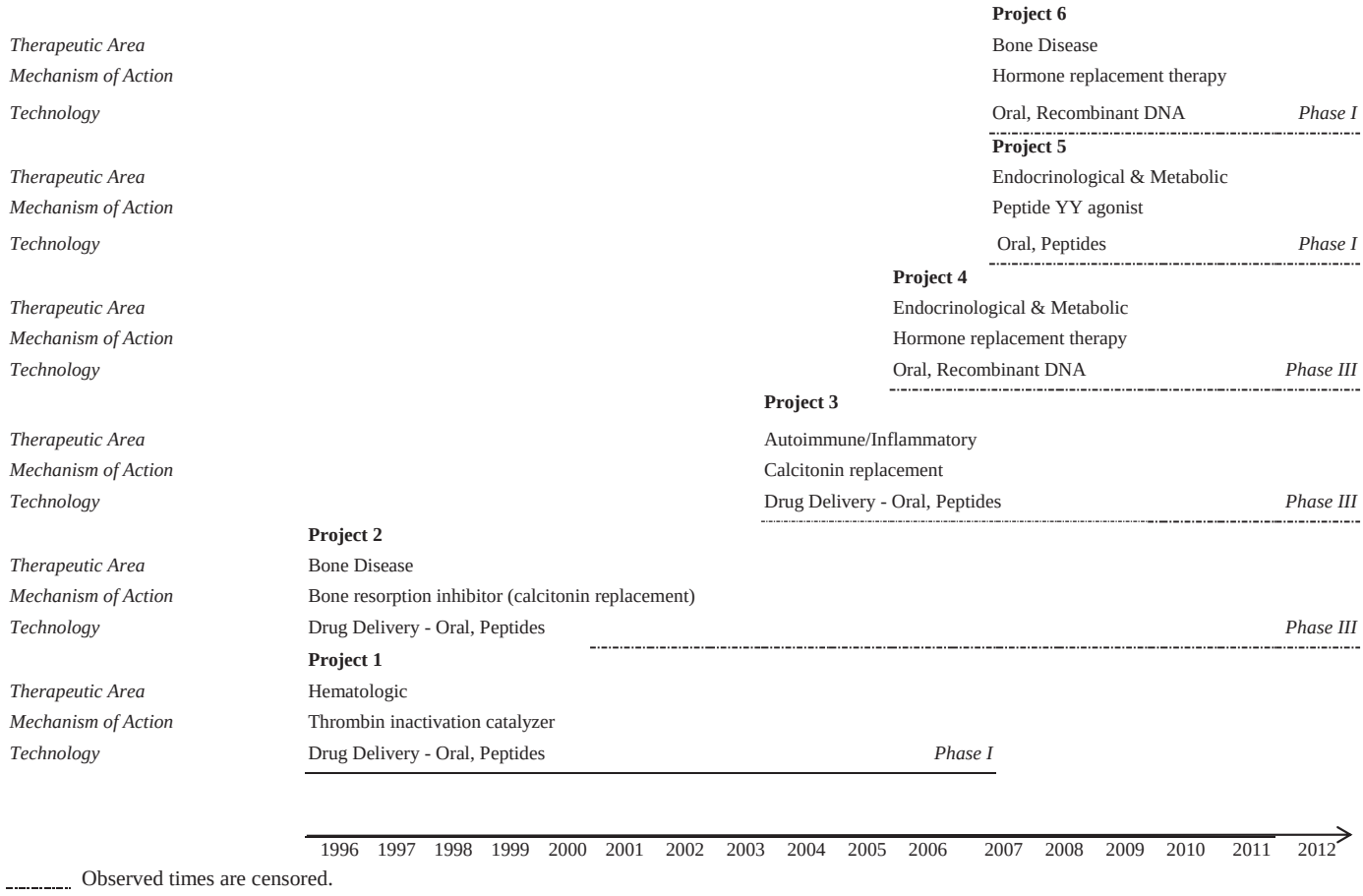

Fig. 3. Example of an R&D project portfolio for one firm in the sample.

3.3.3. Control variables

Project organization. The governance mode for each project was coded 1 for solo development and 0 for collaborative development. According to Pisano (1997), due to information asymmetry combined with quality uncertainty, biotechnology firms tend to offer inferior projects for collaboration while maintaining their more promising projects in-house for solo development and commercialization. *Compound origin* was categorized as follows: coded 1 if the compound was discovered and developed by the target company and 0 if it was in-licensed. According to Evens (2016), for large pharmaceutical firms, success rates are higher for in-licensed than for self-originated drugs. *Novel mechanisms of action.* Firms must build strong evidence to establish the mechanisms of action during the discovery phase. Consequently, the attrition rate for compounds with novel mechanisms of action may be higher than for those with previously established (or precedented) mechanisms of action. According to Kola and Landis (2004, p. 713), "A precedented mechanism of action is defined as one hitting a therapeutic target that a drug in the market place hits, or which has shown proof of concept in late clinical trials." Meanwhile, Biagini, O'Neill, Bray, and Ward (2005) argue that a project containing a new class of compounds with a novel mode of action is unlikely to make it to the clinical development phase in the near future. Consequently, if the mechanism of action was unprecedented, it was considered innovative and coded 1 and coded 0 otherwise. *Therapeutic area.* Because development approaches and project outcomes vary significantly by therapeutic characteristics (Macher and Boerner, 2012), following Hoang and Rothaermel (2010), we created three broad therapeutic area dummies. The two first dummies (Cancer and Infectious) accounted for 66% of the sample, while the third dummy accounted for the 10 other therapeutic areas targeted by the remaining projects. To control for the firms' overall resources, we included firms' *R&D expenditures* and *size* (logarithm of the number of employees) for the year before the initiation of the focal project. Historical data were obtained from the *Compustat* database.

4. Analysis

We tested our hypotheses concerning the effects of project interdependencies on project termination using survival analysis, whereby data are typically subject to censoring (e.g., when a study ends before the event occurs) (Allison, 1984). We estimated a proportional hazard model using Cox's partial likelihood method (Cox, 1972). Unlike discrete time or parametric models, such as Weibull's model, with the Cox model there is no need to identify a specific distinct hazard function. For each project, an event is registered upon termination. The effects in a Cox model reflect the relative effect of each covariate on the survivor function. Given that each biopharmaceutical firm had multiple projects, the assumption of independence of observation is highly questionable in our data. To address this problem, we estimated the Cox model with a robust specification incorporating the Stata *cluster* option to indicate that the observations are clustered. The *cluster* option adjusts the standard errors to allow for the possibility of non-independence across projects initiated by the same biopharmaceutical firm.

5. Results

Table 2 presents the descriptive statistics, and Table 3 presents the Pearson correlations for the variables. We first compared survivor functions and tested for significant differences. Fig. 2 displays the graph of the estimated survivor functions by clinical phase. The Wilcoxon–Breslow–Gehan test is significant, indicating that the null hypothesis

Table 2
Descriptive statistics.

Variable	Mean	Std. Dev.	Min	Max
Project organization	.479	.500	0	1
Novel mechanism of action	.366	.703	0	1
Compound origin	.832	.374	0	1
R&D expenditures (log)	3.629	1.249	−0.151	11.045
Size (log)	2.822	1.060	.405	5.389
Cancer	.531	.499	0	1
Infectious	.102	.302	0	1
Therapeutic areas (other)	.367	.428	0	1
Project year	2003	4.893	1990	2012
Pooled technology interdependence	.767	.492	.034	5
Longitudinal interdependence	.575	.492	0	14
Reciprocal resource interdependence (Phase II)	.446	.445	0	1
Reciprocal resource interdependence (Phase III)	.046	.181	0	1

that survivor functions do not differ must be rejected. The survival function for Phase I projects is consistently lower than for other projects (except at around 130 months). For instance, the probability of surviving for 4 years (48 months) or more is around 0.95 for projects in the pre-clinical phase versus around 0.70 for projects in Phase I.

Table 4 presents the prediction results for project termination. Model 1, with control variables only, shows that project organization, R&D expenditures, and project year significantly affect the hazard rate for project termination. Consistent with previous studies, we find a positive relationship between R&D expenditures and the hazard rate for project termination. For instance, DiMasi (2014) estimates the annual growth rate in pharmaceutical R&D expenditures from 1995 to 2000 at 11.3%, whereas the number of drugs reaching market for all therapeutic indications decreases, at approximately 14.3%. Kola and Landis (2004) find that firms with R&D budgets of less than US$400 million have approximately 18% higher success rates. This could be partly explained by the possibility that smaller companies are more inclined to work on me-too drugs, which should have higher success rates (me-too drugs are products that largely duplicate the action of existing drugs; see Hollis, 2004), and that their portfolios are skewed more towards one therapeutic area over another, with a greater probability of success (Kola and Landis, 2004). Other authors suggest a more complex relationship between R&D expenditures and project performance. For instance, financial resource constraints would not be directly related to project performance or failure but are instead moderated by team attributes such as the team's innovation climate or collaborative approach (Weiss, Hoegl, and Gibbert, 2011).

Model 2 introduces the variables *Pooled technology interdependence* and *Longitudinal interdependence*. Hypothesis 1 predicts that *Pooled technology interdependence* has a negative effect on project termination. The coefficient in Model 2 is not significant, and therefore Hypothesis 1 is not supported. However, the positive and significant effect of longitudinal interdependence (Model 2, $\beta = 0.118$ $p < 0.05$) supports Hypothesis 2.

Models 3 and 4 introduce the variable *Reciprocal resource interdependence*. We tested the direct effects of reciprocal resource interdependence on project termination (Hypothesis 3) for two phases: the consequences of Phase I unanticipated demand on Phase II (Model 3) and the consequences of Phase II unanticipated demand on Phase III (Model 4). The results for Phase III termination show a positive and significant effect of resource interdependence (Model 4, $p < 0.01$), providing support for Hypothesis 3. The results for Model 3, which tests the effect of resource interdependence on Phase II project termination, show that the coefficient is not significant. Resource utilization increases considerably at each phase (Kennedy, 1997). For instance, Phase III studies are large-scale clinical trials that are extremely costly and risky compared to Phase I/II (DiMasi and Grabowski, 2007). Hence, an unanticipated resource demand may have more effect in Phase III. Considering the work that is done during the different phases, projects in Phase II and III have higher reciprocal resource interdependencies than projects in Phase I and II. Consequently, the results provide support for Hypothesis 3.

The results for Models 3 and 4 indicate that projects with novel mechanisms of action have a significantly lower hazard rate for project termination. Drugs are discovered through screening procedures and new mechanisms of action. Although the distinction is somewhat artificial, because new drugs tend to involve novel mechanisms of action (Perucca, French, and Bialer, 2007), the results indicate that projects based on innovative mechanisms of action have lower risk of termination in later stages. Previous studies on innovation have shown that firms that apply more advanced technologies have greater incentive to screen their employees more thoroughly in terms of qualifications and skills (Berman, Bound, and Griliches, 1994). Differences in the firms' ability to recruit and manage intellectual capital can explain the differences in their ability to translate knowledge produced in the scientific community to knowledge that a market will value (Gittelman and Kogut, 2003). Consequently, the probability of project termination is lower for firms with more advanced technologies. Results also show that in-house compounds have a significantly lower hazard rate of termination.

6. Discussion and conclusion

The objective of this paper was to examine the impact of project interdependencies on project termination. We distinguished three patterns of interdependencies that may occur in the drug development process. The hypotheses were examined using data on 417 clinical research projects undertaken by biopharmaceutical companies.

Our results show that only certain types of interdependencies have a significant effect on drug development projects. One might theorize that using common technological platforms would reduce the probability that a project will be stopped. However, the diversity of compounds and diseases is such that clinical trials may be highly idiosyncratic (Cockburn and Henderson, 2001), and the design of each new trial may require specific technological expertise, even when the technology is also used for other projects. In drug development, technologies are not usually limited to individual therapeutic applications. Instead, they serve to facilitate the discovery of new drugs or the R&D process itself (Bode-Greuel and Greuel, 2005). Pooled technological interdependencies between projects that enable firms to extend their technological capacities (allowing several teams to use the same technologies to work on different therapeutic applications) can increase the lead time for new development projects (Pisano, 1996). However, our results highlight a lack of significant connection between pooled interdependencies and the number of such events within a given time period. As Hoang and Rothaermel (2010 p. 747) point out, "The factors that increase the rate of project success do not necessarily decrease the rate of project termination." Moreover, biopharmaceutical SMEs tend to specialize in technology use, which could also explain the lack of connection.

Table 3
Bivariate correlation matrix.

Variable	1	2	3	4	5	6	7	8	9	10	11	12
1.Project organization												
2.Novel mechanism of action	.023											
3.Compound origin	.025	.004										
4.R&D expenditures (log)	.006	−0.033	−0.105*									
5.Size (log)	.256*	.145*	.197*	−0.027								
6.Cancer	−0.093†	−0.041	−0.067	.048	−0.058							
7.Infectious	−0.026	−0.006	−0.100*	−0.017	.066	−0.358*						
8.Therapeutic areas (other)	.113*	.046	.132*	−0.038	.019	−0.810*	−0.257*					
9.Project year	.109*	.024	−0.063	.037	.175*	.033	.125*	−0.113*				
10.Pooled Technology interdependence	.097*	.039	−0.075	.038	−0.134*	.014	.049	−0.045	.009			
11. Longitudinal interdependence	.074	−0.035	.051	.002	.163*	.056	−0.046	−0.026	.008	−0.111*		
12. Reciprocal resource interdependence (Phase II)	.006	−0.096*	−0.106*	.058	−0.132*	.072	−0.020	−0.062	−0.046	.132*	−0.030	
13. Reciprocal resource interdependence (Phase III)	−0.029	.034	−0.038	−0.015	−0.121*	−0.025	−0.025	.042	−0.215*	.045	−0.082†	−0.246*

† $p < 0.10$.
* $p < 0.05$.

In contrast, when earlier projects using the same technology were abandoned, the likelihood of project termination increases. Longitudinal technology interdependencies have more collateral effects on the termination decision than pooled interdependencies. Pooled interdependencies create differentiation niches, whereas longitudinal technological interdependencies create path dependence through lineation management (Berggren, 2019). Project lineage management appears to be a risk-management strategy, in that it enables making decisions about whether or not to pursue a project that is considered risky (Maniak and Midler, 2014; Midler, 2013, 2013). The first project being exploratory, it creates further options that can be exploited in subsequent projects. In this way, the first project plays a determinant role in decisions concerning the project portfolio (Kock and Gemünden, 2019). Technological capabilities that are developed through past experience with a technology are internalized as organizational memory, providing potential capabilities for future projects. Project failures and successes tend to influence this path dependence (Zahra and George, 2002). Cockburn and Henderson (2001) find that past success at the therapeutic class level, as measured by the depreciated stock of past successes, is positively associated with successful project outcomes. Abandonment and failure may stem from a history of technological failure. Factoring in longitudinal interdependencies makes it possible to understand project history and the dynamic nature of the organizational context, and hence to develop the sequence-related management capabilities needed to handle this dynamism (Khanna et al., 2018). In such cases, Kock and Gemünden (2019) consider that project lineage management is reactive. In an examination of project lineage management in large enterprises operating in various industries, Kock and Gemünden (2019) show that reactive lineage is significantly related to all dimensions of success in a project portfolio (strategic fit, average product success, synergy exploitation), except for portfolio balance. Our results suggest that, in the case of reactive lineage, the termination decision must take into account uncertainties in future technology performance. This makes it harder to maintain a balanced project portfolio.

Our results also suggest that reciprocal interdependencies most probably affect which human resources are assigned to projects in a portfolio, confirming the importance of resource planning. As Jekunen (2014 p. 2012) points out, “Before undertaking a development project, the organization should ensure that it has planned thoroughly and that it has adequate resources in place.” This is all the more important given that exploration projects are conceived as experimental learning processes that are not necessarily subject to formal planning. However, a shortage of resources due to poor anticipation of success rates during the R&D process can cause project termination. Indeed, in the biopharmaceutical sector, human knowledge and expertise are the most critical and scarce resources (Dickson & Gagnon, 2004). Consequently, human resources management cannot be determined by isolated requests from individual projects (Thiry and Deguire, 2007). Instead, a systematic, proactive approach that reflects the entire project portfolio environment is needed. Proactive lineage enables balancing the project portfolio with a view to increasing the company’s capacities so as to cope with the opportunities that knock and the risks that they entail (Kock and Gemünden, 2019).

Resource interdependencies therefore have complex effects on the R&D process and on project success or termination. On the one hand, resource interdependencies associated with poor resource anticipation lead to project termination. On the other hand, freeing up resources due to terminations would have the beneficial impact of accelerating other compounds in the pipeline. Girotra et al. (2007) show that terminations that occur when the Phase II success rate in the firm’s pipeline is higher than expected act to accelerate projects on other compounds in the pipeline, thereby lessening the impact of these failures on the firm’s value.

Termination decisions can be interpreted in terms of Lindblom’s (1959) concept of “muddling through.” In other words, means and ends are necessarily interrelated in decision-making processes, which aptly describes how complexities are handled in projects. Put another way,

Table 4
Predicting project termination: results of Cox model estimations with cluster observations.

Variables	Model 1	Model 2	Model 3	Model 4
Project organization	−0.389†	−0.397*	−0.379†	−0.792*
	(0.214)	(0.214)	(0.209)	(0.427)
Novel mechanism of action	−0.067	−0.052	−0.261†	−2.80***
	(0.158)	(0.160)	(0.143)	(0.575)
Compound origin	−0.151	−0.160	−0.211	−0.982
	(0.220)	(0.223)	(0.361)	(0.748)
R&D expenditures (log)	.322*	.285†	.732*	.598
	(0.157)	(0.160)	(0.321)	(0.670)
Size (log)	−0.143	.068	−0.093	.206
	(0.232)	(0.128)	(0.230)	(0.516)
Cancer	−0.086	−0.110	−0.243	−0.997
	(0.167)	(0.168)	(0.222)	(0.665)
Infectious	.312	.312	.197	1.266*
	(0.277)	(0.278)	(0.354)	(0.560)
Project year	−0.092***	−0.091***	−0.149**	−0.249*
	(0.017)	(0.021)	(0.051)	(0.112)
Pooled technology interdependence		.118		
		(0.156)		
Longitudinal interdependence		.110*		
		(0.048)		
Reciprocal resource interdependence (Phase II)			1.112	
			(1.079)	
Reciprocal resource interdependence (Phase III)				3.813**
				(1.242)
Log likelihood	−1069.632	−1065.431	−510.677	−56.456
Wald chi2(4)	75.49***	80.53***	60.61***	22.76**
N	417	417	226	43

Robust standard errors appear in parentheses.
† $p < 0.10$.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.A positive (negative) coefficient sign indicates a greater (lower) hazard of the focal event occurring (project termination). This means that the variable of interest leads to a faster (slower) occurrence of the focal event (Allison, 1984).

just as we can't know what will work, we can't be certain of what will not work. For instance, Buonansegna et al. (2014) distinguish between false-negative failures, false-positive failures, and positive/inevitable failures, all of which may have different causes and different impacts on a firm's portfolio value. Moreover, Martinsuo (2013) argues that one way to view portfolio management is a negotiation and bargaining system arising from decisions based on previous projects. However, this system may become more complex when, in the case of the drug development process, failures occur for given indications but can become successes for others.

This leads to the limitations of this study. Stopping a project is not necessarily a failure, for several reasons. First, project termination can lead to project suspensions. A project can fail when information indicates that the only rational option is to cancel the project. When the decision is less clear cut, however, a project may be suspended, or stalled in a buffer, only to continue at a later date (Cooper and Edgett, 2012). Previous terminated projects are key indicators for the future value of entrepreneurial firms. According to Hu, McNamara, and Piaskowska (2017), prior project termination can have different effects on abnormal returns, depending on whether the project fails or is suspended. Future studies could enrich our initial findings on the distinction between failure and suspension. Furthermore, due to the nature of the data, this study does not address the underlying decision-making process or the manner in which managers draw on previous projects to manage interdependencies between projects. Future studies could investigate decision making concerning project management lineage. In addition, the causes of project termination should be analysed, and while considering the causes of project termination, the consequences for long-term organizational performance should be investigated.

6.1. Managerial implications

The biopharmaceutical industry may serve as a model for firms in other industries that share the same contingencies in a highly dynamic and competitive environment. As Khanna et al. (2018) points out, terminations can be strategic for shaping innovative portfolios: "Interdependencies in research portfolios may influence not only the effectiveness of search, but also firms' selection strategies" (2018, p. 2459). The results of the present study offer new insights into project portfolio management practices. Managers are recommended to adopt a dynamic perspective and to combine project portfolio management with project lineage management. This means that decisions about the project portfolio structure need to consider more than just project interdependencies at a given moment. Because projects evolve over time, they require the development of evolving knowledge management systems, such as using learnings from past projects (Kock and Gemünden, 2019) in order to optimize investments in future projects. At the same time, managers should build the firm's exploration capacity so it can leverage new technologies for subsequent projects.

In addition, better predictions of success rates along the pipeline could help optimize project portfolio management by improving the decision-making process. Known as proactive project portfolio management, it is considered a more effective management style. By judiciously allocating and reallocating resources horizontally across projects, firms can send a positive signal to investors through their effective use of potential resources and sound management, both of which create value (Hu et al., 2017). Finally, managers should be aware of the potential psychological and cognitive factors that may precipitate the decision to initiate or terminate a project.

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