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Review

# Erosion of the principal investigator role in a climate of industry dominance

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**Abstract**

The academic investigator who was central to the development of anticancer therapeutics during the first several decades of that ushered in oncotherapeutics must now contend with working side-by-side with the pharmaceutical and biotechnology industries who are dominating the scene. However, the relationships between industry and academic investigator are often strained, largely because of their incongruent and competing interests. Although the pharmaceutical and biotechnology industries are now developing some of the most exciting therapeutics to come along in many years, the academic investigator is facing a loss of autonomy and creativity, which may have been responsible for the successful development of many anticancer agents that would have not been developed in the present environment. This commentary discusses the impact of the pharmaceutical and biotechnology industries on the academic investigator, new challenges, and potential threats to optimal therapeutic development.


*Keywords:* Drug development; Pharma industry

Although institutional review boards, regulatory agencies of government, and the scientific community at large consider the principal investigator as the individual who is ultimately responsible and accountable for the design, execution, and analysis of clinical trials of novel therapeutics, the role of the academic investigator is becoming ''dangerously ambiguous'' [1–7]. There is no doubt that the phenomenon is largely due to the progressively greater role that the pharmaceutical and biotechnology industries are playing in drug development. The heightened interests of the pharmaceutical and biotechnology industries in cancer therapeutic development, along with the somewhat ''seasonal'' investment community have undoubtedly catalysed cancer therapeutic development efforts over the last decade. However, the involvement of these new forces, with their inherent pressures to show almost immediate gains to their shareholders and who have limited attention spans with short-term interests, have transmitted a new series of pressures to clinical investigators and have modified the very nature of clinical research at academic institutions. Now, the investigators are concerned about the same short-term pressures as the corporate world such as inordinately difficult timelines for study completion and pressures to demonstrate antitumor activity as early as possible. Once upon a time, when industry was not interested in the development of cancer therapeutics, clinical researchers had once become ''one with their drugs'' by knowing and experiencing the smallest toxicologic, pharmacologic, and esoteric detail, perhaps by even personally evaluating the majority of patients who received the agent in the early stages of drug development. However, it is evident that clinical cancer researchers/drug developers at academic institutions are becoming smaller and smaller cogs in larger and larger, industry-sponsored multi-institutional studies that are in part designed to fulfill overly ambitious corporate

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timelines and short-term interests of the investment community. Although the notion of the principal investigator or clinical researcher as the "captain of the ship" and primary proponent for the optimal development of new anticancer agents may seem somewhat romantic – "yearning for the way that things used to be" – as well as self-serving, we must address whether this evolution in the responsibilities of the principal investigator represents a deleterious shift towards the suboptimal development of new anticancer therapeutics.

From the standpoint of the principal investigator, the relationship between the pharmaceutical and biotechnology industries is one of both love and hate. On one hand, the renewed interests of these industries in cancer therapeutic development have resulted in the acceleration of applied sciences and the entry of a wide variety of high-quality therapeutics into our pipelines. However, the pressures and inherent objectives of the 'business of oncology' have interfered with the true role of the principal investigator, which may have an impact on the optimal development of cancer therapeutics on both microscopic (*i.e.* individual studies) and macroscopic (*i.e.* overall drug development paradigm) scales. The early years of anticancer drug development in the United States and elsewhere were largely dominated by efforts sponsored by governmental agencies, particularly the National Cancer Institute (NCI). During this period, principal investigators became "attached" to therapeutics and the proponent for their optimal development, often shepherding them through an unencumbered process. Commercial concerns were relatively non-existent and, therefore, the focus on large markets and other factors that currently play a major role in steering disease-directed evaluations were not operative. Instead, disease-directed drug development was more in line with observations from fastidiously conducted phase 1, phase 2, pharmacologic, and translational studies, as well as with the alignment of clinical development with preclinical observations. The NCI development process encouraged 'foundation building', in which clinical scientists orchestrated both clinical and translational studies autonomously, and each subsequent stage of an agent's clinical development was based on the results of bedside and laboratory investigations performed during a prior previous stage. Investigators and institutional programs often conducted the foundation building independently and such processes resulted in them developing intimate relationships with their compounds. The clinical investigator was truly the 'captain of the ship,' often navigating the overall development of new agents through preclinical, phase 1, and disease-directed studies. If there were any questions about specific toxicities or developmental directions, the dictum was to go directly to the investigator. The investigator held clinical data close to hand and was often aware of and encyclopedic about all pharmacokinetic, translational, and clinical data generated about any particular agent. More importantly, the results of preclinical and clinical investigations ware often discussed and debated in an unimpeded, uncensored fashion at major meetings. Very little was withheld on the basis of non-scientific interests.

However, a brave new world is upon us. At present, the principal investigator performs studies on the majority of anticancer agents, even the most uncomplicated phase 1 trials, as a small cog in a large clinical trial machine, often not having played an integral role in the formulation of the clinical development plan at either the macroscopic or microscopic levels, and often not even understanding the principal objectives of the plan. Once a captain of the ship, the infrastructural aspects of these trials are now dominated by large Clinical Research Organization (CRO) and multiple autonomous factions of pharmaceutical companies (*e.g.*, experimental medicine, product oriented medicine, marketing, regulatory, business unit, pharmacology, quality assurance, and imaging groups), each of which enacts its own standard operating procedures and insists that the investigator work according to their directives in the name of Good Clinical Practices (GCP). This fractionation has undisputedly resulted in a true loss of control by the principal investigator for even the most insignificant facets of the clinical trial. Ironically however, the principal investigator is still considered ultimately responsible for the trial conduct by Institutional Review Boards and regulatory authorities. Nevertheless, it is now common practice to assign the principal investigator for a multi-institutional studies after the conclusion of the study, often by proxy or arbitrary irrelevant criteria such as the investigator who accrued the largest number of patients instead of participating in the crucial aspects of study design. Interestingly, both investigators and institutions have largely accepted this practice, possibly due to concerns that they will not be offered study participation if they refute such practices. In essence, this complacency enables sponsor and/or CROs to more readily control both microscopic and macroscopic aspects of large and small clinical investigations.

From the standpoint of the individual investigator, trying to grasp the organisational aspects of the pharmaceutical sponsor, dealing with internal flux in these dynamic organisations, and contending with the paperwork, often generated in the name of GCP, has become an inordinate task. Although the organisational structure of less complex, smaller biotechnology companies might be much easier to grasp and navigate, the financial and timeline pressures inherent in the survival and growth of smaller companies are more transparent and closer to the academic scientists involved with clinical trials. These pressures are often transmitted to the investigator and the clinical trial itself. Concerns about market/investor perception of new therapeutics are

progressively dominating decisions made in early clinical trials and these pressures are often palpable to the investigator, even in the earliest developmental stages of new compounds. For example, although the participation of patient populations with refractory cancers known to have excellent performance status and ideal for the evaluation of toxicity in phase 1 studies, the participation of such patients is now considered suboptimal since subliminal corporate pressures have shifted clinical study goals and designs towards maximizing the potential to demonstrate clinical activity in order to prop up the drug's perception in investment community. Such efforts, which are often based on teleological reasoning and misperceptions about the mechanism of action of new drugs, are impeding the optimal achievement of the principal toxicological objectives of these trials. In other words, phase 1 trials are progressively incorporating efficacy endpoints – both outright and subliminally.

Sponsors have become obsessed with meeting timelines and milestones, and this obsession is indeed coming at a cost. The single institution, single principal investigator trial is becoming archaic due to the notion that timelines are much more likely to be met by using more investigators and institutions, even when it is clear that the bottleneck is study design, not patient accrual. Championed by the pharmaceutical and biotechnology industries, the growing trend in conducting phase 1 studies is in the direction of large, multi-functional evaluations in lieu of smaller, more intimate trials that have been traditionally conducted at a single institutions and strictly focused on dose finding and characterising the toxicological and pharmacological profiles of new anticancer therapeutics. This trend undoubtedly stems from mounting competitive pressures in these industries, resulting in a quest for maximal efficiency in patient resource utilization and a strict adherence to often unrealistic timelines driven by upper management. These competitive corporate pressures have been progressively shifted over the years to the clinic and are now being observed downstream at the earliest phase of therapeutic evaluations. These were once considered immune from any study design imperfection that would even slightly increase the risk for patients, since the overriding theme in the design and phase 1 studies conduct has always been related to minimizing risk where the principal dictum has been to cut no corners and leave no stones unturned. The phase 1 studies of anti-cancer agents, which have much narrower therapeutic margins and higher risk-benefit ratios than new agents in other therapeutic disciplines, have traditionally been performed by a small number of experienced investigators at a maximum of one or two highly specialised study sites. This practice once encouraged investigators to become intimate with their clinical and pharmacologic data, whereas current multi-institutional practices encourage investigators from different sites to compete with one another for treatment slots. The Good Laboratory Practices (GLP), which mandate the use of the fewest well calibrated instruments as possible to minimise experimental variability inherent in instrumentation. Similarly, the seemingly minor, albeit powerful, characteristic of the intimate study has traditionally facilitated the acquisition of expertise by both investigators and research staff, since it enables them to make detailed observations over the entire range of dose levels. Not only does the resultant intimacy enhance the ability of investigators to detect subtle, but potentially consequential, adverse effects, and to readily compare toxicities from dose level to dose level, patient to patient, and schedule to schedule, but the geographic concentration of adverse events has undoubtedly accelerated the derivation of measures to minimize adverse effects, which would have otherwise led the development of many important therapeutics astray for many years or possibly forever. In essence, this rather low-tech approach to phase 1 evaluations has resulted in the accurate, safe, expedient, and successful characterization of the toxicological and pharmacological profiles of a wide array of anti-cancer agents over the last several decades that, in the absence of such measures, may have otherwise been placed back on the shelf. Even more concerning is the lack of real-time sharing of data by sponsors who insist on the use of central laboratories and do not permit investigators to perform pharmacokinetic and translational analyses at their own sites. This practice is often justified under the guise of the somewhat questionable need for data analysis at commercial laboratories that abide by 'GLP' when the real issues are control of the data and data confidentiality due to perceived competitive pressures. Furthermore, such information is often held 'close to chest' under the guise of irrelevance or until the data, itself, are irrelevant. Should not the 'captain of the ship' be able to decide on the relevance of all study data in a real-time fashion, and why are not principal investigators complaining about the lack of availability of all clinical, pharmacological, and translational data during the course of multi- and single-institutional trials when the sponsor is often cognizant of such data? In some cases, sponsors have even refused to disclose chemical structures and preclinical information, construed as highly proprietary, to the principal investigators. However, maybe an even more important concern is that investigators are no longer questioning these practices, even though they bear the ultimate responsibility for the conduction of the trial. Undoubtedly, many investigators fear that future relationships depend on their perception as well behaved investigators who are not prone to troublemaking behavior. Certainly, this complacency is coming at a cost in terms of optimal study design, processing of the results, and overall drug development.

Sponsors are recognized lawfully as the true proprietors of novel therapeutic, intellectual property, and pat-

ents, and public companies do have fiduciary responsibilities to their shareholders. However, both investigators and sponsors must consider ethical and moral issues that pertain to whether their obligations extend to society at large, particularly when their proprietary technologies may portend reasonable benefit to cancer patients. As a society, we must address whether sponsors of precious medical commodities like cancer therapeutics should be allowed to make irresponsible developmental decisions, strictly based on financial and proprietary concerns. In other words, once an invention is known to have a reasonable likelihood of impacting society, particularly in ameliorating pain and suffering, does the inventor then become obligated to optimally and expediently develop the invention? Should the ramifications of decisions pertaining to such inventions, patents, and intellectual property of such medical importance be considered similar to those of companies that produce, develop, and market video games, cogs, and widgets? Or, should pharmaceutical and biotechnology sponsors be held to a higher level of responsibility for decisions that ultimately lead to suboptimal results in terms of delayed remedies for the ailing and suffering? On the flip side, should their rewards be disproportionately greater than sponsors of other products if they are to be considered disproportionately more culpable for suboptimal results?

Sponsors and investors formulate commitments with investigators and institutions with the underlying assumption that they will fulfill the principal goals of the studies, but the 'small print' in study site contracts often gives them "an easy way out" (*i.e.* early study termination) when the "going gets tough" – for example, when developmental risks appear inordinate, when agents do not appear to be suited for the most profitable common tumor types, or even when there are no responses in phase 1 evaluations. In addition to commitments to investigators and institutions, do both sponsors and investigators have underlying commitments to patients who took part in the earlier stages of the study to meet the overall study goals? Premature study termination based on fiduciary concerns can be construed as a violation of this unwritten contract in which the research patient assumes that the drug will be developed to its fullest irrespective of financial concerns. Certainly, the pockets of the pharmaceutical and biotechnology industries are limited, but potentially active drugs should not be put on shelves solely due to financial and proprietary concerns. Perhaps, mechanisms should be formulated and even mandated whereby individuals, institutions, and government agencies can further study such therapeutics, with partial licensing rights retained by the original sponsor. Once a compound becomes a "therapeutic" with a reasonable potential to benefit even patients with orphan diseases, sponsors can then assume heightened responsibilities and obligations. Investigators must speak up when such issues arise and must never allow themselves to become complacent when faced with the erosion of their responsibilities in true spirit of a principal Investigator. It is clear that a committed principal investigator who is truly aware and responsible for all aspects of their clinical trial will benefit patients, institutions, sponsors, and overall therapeutic development against cancer.

The public benefits incalculably from industry funding of biomedical research. The importance of nurturing academic–industry relationships is clear, but so is the potential for problems, resulting in suboptimal therapeutic development, if those relationships are not managed wisely. The importance and role of the principal investigator is undoubtedly dwindling and, although the pressures and practices of sponsors are partially to blame, the complacency and passivity of academic investigators are ultimately responsible and culpable. It is clear that consensus-building among academic investigators worldwide, resulting in the adoption of clinical trial standards would help both institutions and sponsors structure partnerships to be both ethical and productive, resulting in the optimal and most expedient development of anticancer therapeutics.

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