SCREENING FOR NEW CHEMICAL ENTITIES IN ACADEMIC SETTINGS

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Introduction

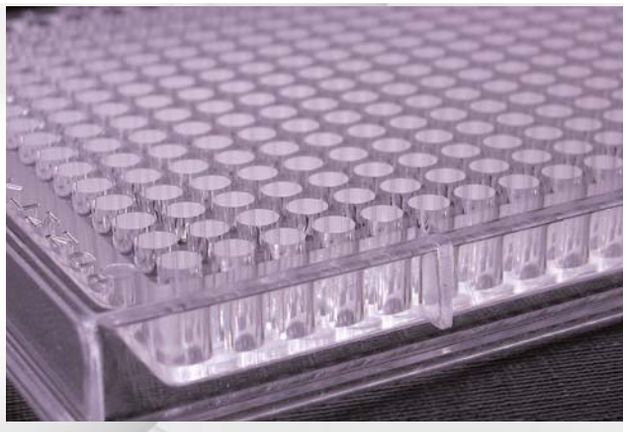
Large pharmaceutical companies with significant financial leverage were the pillars of drug development in the mid- to late 1980s. Two predominant factors influenced the rate of success in this field: resources and access to financial capital. Large organizations such as Pfizer, Wyeth and Bristol Meyers Squibb had both elements. In the mid-1990s, numerous New Chemical Entities (NCEs) were discovered and marketed. Financial success was synonymous with drug development. Indeed, the mid-1990s served as the "golden years" for pharmaceutical companies. Some companies such as Pfizer saw their stock value balloon within a short period of time.

However, in 2008, the picture is anything but rosy for pharmaceuticals. Most large traditional pharmaceutical companies (excluding biotech companies) have seen their stock decrease markedly from the "golden years." What caused this change and who are the new beneficiaries of drug development programs? The concept that only pharmaceutical companies develop and test new drugs is changing. The paradigm has been shifting to academia and other nonpharmaceutical entities. With extremely low drug development success rates, pharmaceutical companies have been outsourcing research to foreign countries with scientific expertise and to academic research organizations.

From 1991–2000, 23% of the drugs that survived Phase I, II and III trials were not approved by the FDA (1). Nearly one quarter of the drugs that were tested in expensive large, double-blind human clinical trials failed to produce any revenue for the company that invested in the development of that drug. This does not include those drug candidates that failed in Phase I or II trials. Only about 11% of all drug candidates that make it to the clinical trial phases obtain FDA approval (1). With these low success rates, pharmaceutical companies have reevaluated their business models and development needs. As a result, drug discovery and development are taking place in other settings.

Moving Screening and NCE Development into Academia

Academic institutions provide a twofold advantage. First, labs specializing in a particular area of research have a profound understanding of mechanisms and overall knowledge to advance a compound through multiple stages. The expertise may be pivotal to the success of any particular compound. Second, academic research organizations employ numerous postdoctoral fellows and other individuals with a high degree of expertise who are generally not compensated at the same level as pharmaceutical researchers in large organizations.



Hence, this approach meets the scientific and business needs to propel compounds through the pipeline and reduce development costs.

Development costs have been quoted as high as 1.7 billion dollars for an NCE when discovered solely by a pharmaceutical company, almost double the widely accepted $897 million estimate published by the Tufts Center for the Study of Drug Development (2). Increasing failure rates in clinical trials are thought to be driving increased drug development costs (2).

New York Area Bioluminescent Screening Symposium

Promega hosted a bioluminescent-screening symposium on May 2, 2008, for researchers in academia within the New York City, USA, area. Approximately 50 researchers from Columbia University, Rockefeller University, Albert Einstein School of Medicine and several other prestigious institutions attended. Attendees got a firsthand view of the type, quality and quantity of research taking place within the NYC area. The goal of this symposium was to educate researchers on the diversity of research and the techniques used to fully achieve their research potential. Additionally, this served as a forum for Promega to display the tools and techniques that are available to aid in the research and streamline the workflow process.

In addition to academic research organizations, small start-up companies with access to capital such as Ingenious Targeting Laboratories (ITL) were present at the forum. ITL is currently engaged in numerous pharmaceutical development programs focused on developing novel treatments for cardiovascular diseases, immunological disorders and skin diseases. Hence, the goal of this seminar was not just to target academic research organizations but all involved with

the discovery process for novel drugs and therapies. This all-encompassing forum provided insight not only to research but also served as a platform to share and exchange ideas and research techniques.

Summary

Large pharmaceutical companies have begun to outsource numerous projects in the hope of expediting the discovery of future NCEs. Significant potential exists in the exchange between corporate and academic laboratories for learning, developing and sharing ideas, technology and strategies for answering fundamental biological questions, conducting translational research, and developing useful therapeutics.

References

1. Lowe, D. (2004) In the pipeline. **http://pipeline.corante.com/archives/2004/09/20/drug_development_the_current_odds.php** (accessed August 26, 2008)
2. Mullin, R. (2003) Drug development costs about $1.7 billion. *Chem Eng. News* **81**, 8.

SYMPOSIUM SIDEBAR: IN VIVO IMAGING

NON-INVASIVE BIOLUMINESCENT IMAGING IMPROVES UNDERSTANDING OF TUMOR BIOLOGY

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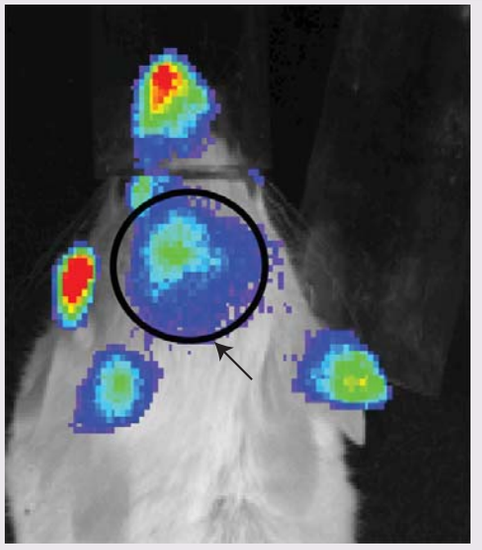
Gliomas and medulloblastomas are the most common primary brain tumors in adults and children, respectively. Although the standard of care for gliomas may have evolved slightly over the last 50 years, the clinical outcome of this disease remains unchanged. Therefore, further research to improve the treatment modalities is urgently needed. An important step forward is the development and validation of mouse models that accurately recapitulate the complexity of human tumors.

This effort has been greatly facilitated by the development of preclinical imaging technologies such as bioluminescent imaging (BLI). A reporter mouse line can be engineered to express luciferase from a promoter that responds to a specific biological process. Luciferase activity can be measured in vivo and correlated with the strength of the pathway driving the transgene construct. For example: we know that the E2F1 promoter is regulated by Rb in cell cycle progression and appears to mediate tumor-selective transgene expression in tumor cells. Therefore, the human E2F1 promoter was used to drive the firefly luciferase gene in a transgenic mouse model. Another reporter line was generated based on the fact that SHH is activated in a subset of human medulloblastoma. In this reporter construct, luciferase is driven by a promoter responsive to Gli, which is a downstream element in the SHH pathway.

Such reporter lines can be used as tools for discovery, revealing pathways previously not recognized as being active in specific tumor types. For example, using the Gli-luciferase reporter mouse, we have demonstrated that the SHH pathway is active in PDGF-driven gliomas. We routinely use luciferase reporter lines for more accurate and detailed measurements of biological processes in preclinical trials by radiation- or chemotherapy. The imaging results from BLI must be validated with histological analysis of tumors. Brain tumors, especially gliomas, are highly heterogeneous, and there is high variability in response to different treatment modalities. Non-invasive imaging with BLI provides a significant advantage and allows each one to serve as its own control. BLI is less expensive than other small animal imaging technologies such as MRI and PET imaging. Finally, the tumors that have been generated in reporter lines also can be used to generate cell culture for in vitro studies; cells isolated from those tumors can be cultured, and BLI can be used to monitor the activity of different pathways.



The Gli-Luc reporter mouse can be used for monitoring PDGF-induced gliomas in mice in vivo. Black arrow points to the tumor.