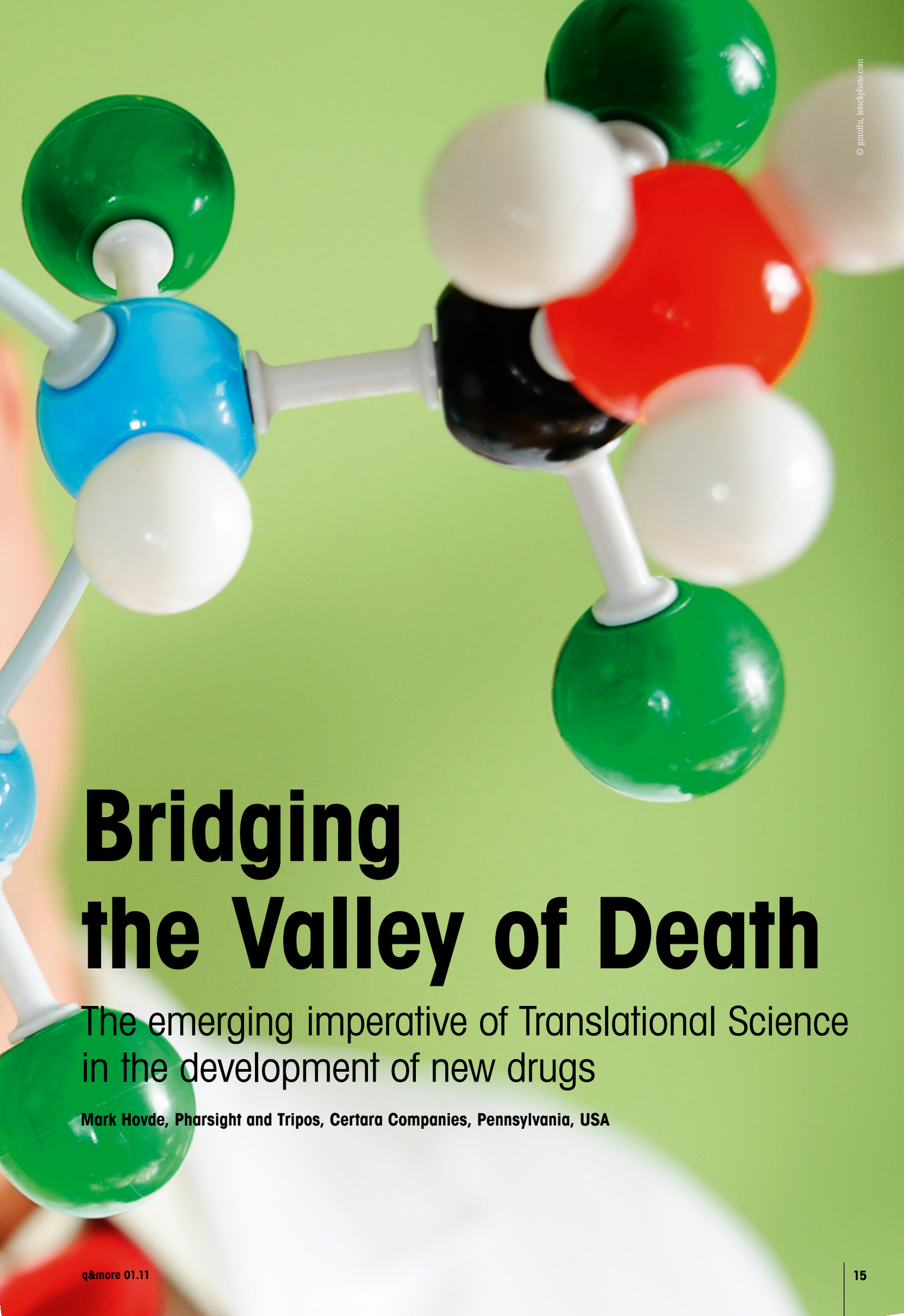


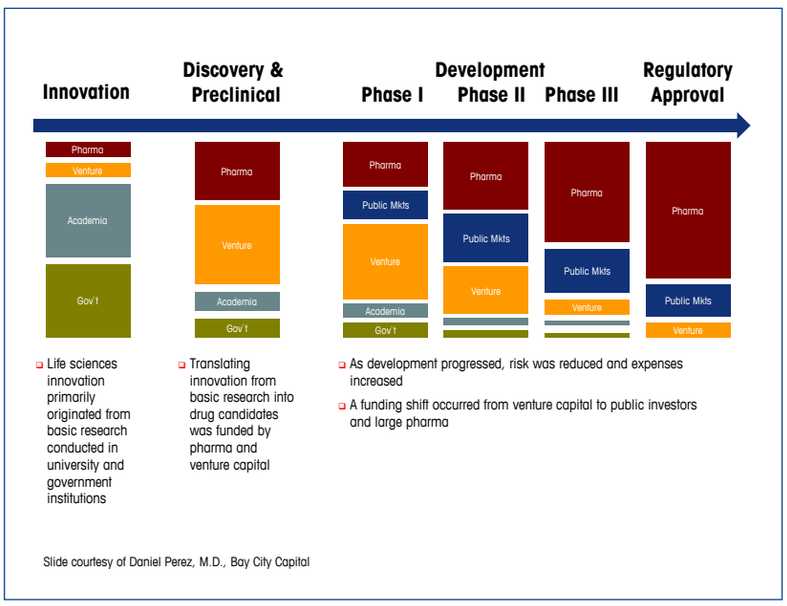
Bridging the Valley of Death

The emerging imperative of Translational Science in the development of new drugs

Mark Hovde, Pharsight and Tripos, Certara Companies, Pennsylvania, USA

Most managers of pharmaceutical R&D define "translational science" as the translation of science to clinical practice by using novel means of analysis, allowing one to make inferences about the performance of a drug candidate much earlier than traditionally organized research would allow. Fundamentally one takes information that is inexpensive to acquire and available early, and uses it to predict something about drug performance that would otherwise require much more time and expense to learn through traditional methods. Thus the cost and time to reach decisions is reduced, and, critically, late stage attrition is reduced because better candidates are advanced to the clinic. Examples of translational science in current practice are very broad and include allometric scaling, use of biomarkers rather than traditional clinical endpoints, and individualization of dosing based on genetic profiles.

Fig. 1 The Traditional R&D Paradigm



The promised land

The promise of translational science arises at a time when funding pressures are the worst in memory at the discovery/preclinical interface. Discovery/preclinical is not the only stage where translational science can make a contribution, but it is an important stage. Some have termed the funding gap at discovery/preclinical the "valley of death" (Fig. 1, 2). Innovation is still happening (see left of Fig.1 and Fig. 2). Some say innovation is even accelerating with the "omics" explosion flowing out of academic and government labs, but in the current state (see right of Fig. 1 and Fig.2) discovery and preclinical funding is shrinking, creating a valley of death between innovation and late stage development. Pharma, venture, and public market/IPO funding, which formerly provided ample money for commercializing promising new innovations, have all shifted from high-risk early- to lower-risk-late-stage development. Thus pharma and biotech companies must find new ways of working if compounds are to progress through the valley of death and live to see the promised land of late stage clinical and registration.

Intellectual challenge

The intellectual challenge of translational science is formidable because there are potentially many aspects of drug safety and efficacy that one might wish to predict from information available early in discovery or development. Uncovering new predictive relationships and making them useful in real projects is often an integrative, iterative, and exploratory process. There are many candidate relationships that use data collected in various research silos and organizations, and many unproductive paths. To be effective, the translational scientist needs new IT tools, something that his silo-focused research IT does not easily provide: seamless feedback systems or loops so that the scientist can rapidly investigate multiple translational hypotheses, confirm or deny relationships, document them, and discard or pursue.

The new reality imposed by the capital markets is driving long-anticipated change across all aspects of the drug development enterprise. Commercial organizations are becoming more collaborative to share risk. For example, Pfizer and GSK recently established a joint venture to develop HIV therapies. Large pharma is developing strategic partnerships with key academic centers, not with grants to fund unrestricted research as was common in the past, but with options-based money to gain access to new science and molecules. Pfizer is sharing IP with certain academic centers in return for options on later development, is launching new precompetitive collaborations, is stepping up in-licensing spend, and is empowering R&D managers to reallocate internal budgets externally if justified[1].

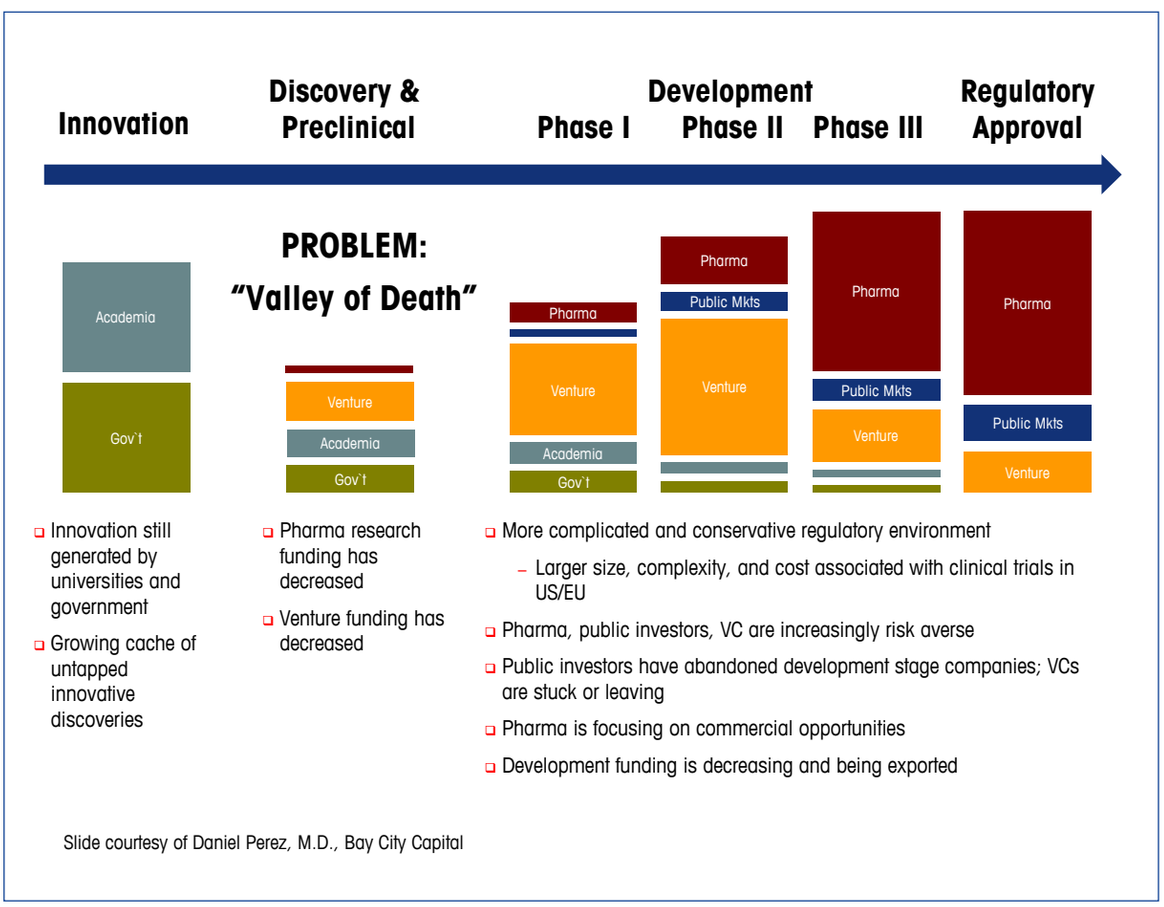
Essential change

We are also seeing organizational change. Translational Medicine groups have been established both in academia and industry with the mandate of improving the translation of the wealth of new data into new medicines for the treatment of human disease. At least 39 pharma and biotech companies have established at least some formal accountability for "translational medicine[2]."

Government is also responding to the new environment by reorganizing and redirecting funds and resources. The NIH has launched its Roadmap for Medical Research ($498M of funding in 2008) and plans to have 60 funded sites operating by 2012. FDA has published the Critical Path document[3] and has initiated numerous projects aimed at improving the "translation" of innovation into therapy. Within the CDER organization FDA has established the Office of Translational Sciences.

Re-organizational is probably a necessary but not sufficient condition for enabling translational science. Further changes will be needed to overcome the many impediments to translational approaches. Existing budgets, priorities and reward systems are set by multiple different departmental managers in large organizations. This may work against translational initiatives and lead to sub-optimization of the entire system. In addition, scientists see problems from their own perspectives, read different journals, go to different conferences, speak with different jargon, and prefer different mental frameworks and tools according to their academic training. This may inhibit communication and knowledge sharing. Finally, information does not map from silo to silo and is collected without an overall master plan (Fig. 3). Diverse data sets needed for translation must be mapped *ad hoc*. Data sets are not linked and cannot be easily retrieved and analyzed. As a result, much useful analysis is never done (it takes too long), and *ad hoc* efforts are hard to re-use, replicate, and teach. In analytics and modeling – the science of extrapolating conclusions from work done in one silo to another, and ultimately from R&D silos to the treated patient in the market,the scientist must have special (and scarce) expertise in math, careful judgment, and profound understanding of the limits of inference.

Fig. 2 The Current State of Pharmaceutical R&D



Approach

A number of IT vendors are investigating solutions that bridge the valley of death through improved data integration enabling translational science. Our Company[4] believes viable solutions enabling translational science will share the following key characteristics:

Economy of storage.
Translational Science solutions will not seek to replicate storage of existing datasets, but rather will permit seamless browser-type access to scientists across the enterprise.

Graceful integration of scientific data and relevant metadata. Translational science requires much more than just integration of datasets. Scientists need access to important information on the context and limitations of data in order to make rational and useful interpretations and inferences.

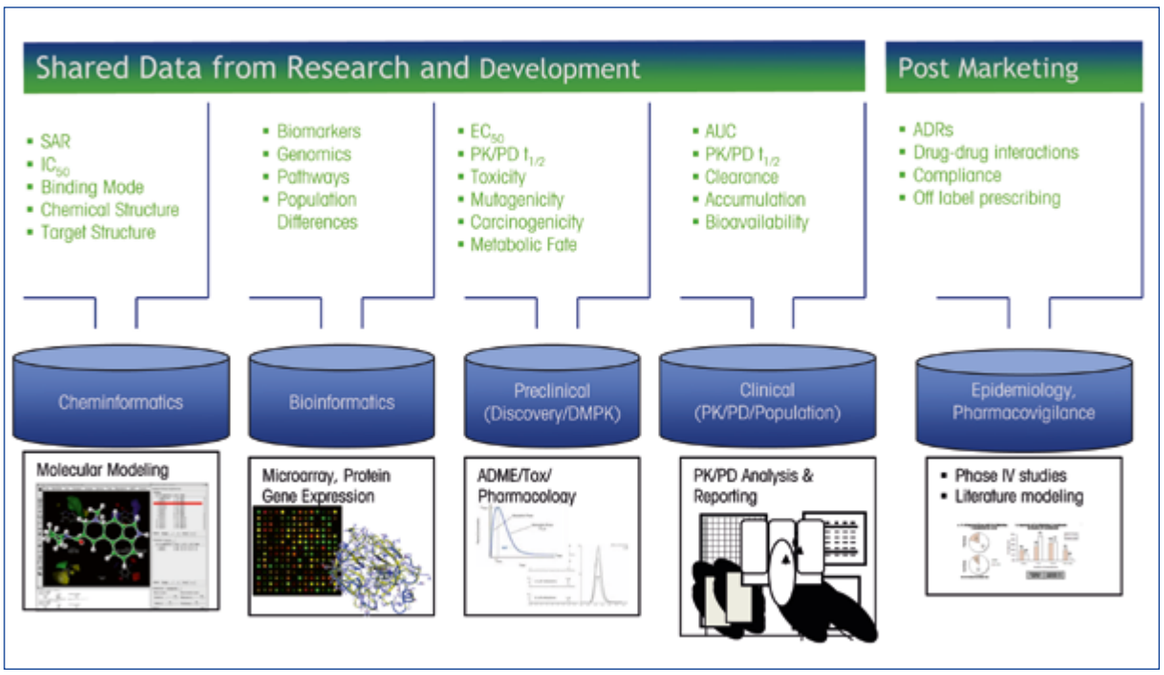
Flexible, capable, and easy-to-use query engines. Translational science will not occur if queries are too cumbersome and time consuming. Building queries must be easy and intuitive, with the query itself requiring no special scientific expertise. Response times for queries drawing from multiple datasets must be comparable with internet-type searches – at most, a few seconds.

For example, consider a compound with an emerging safety issues (e.g., liver toxicity) in the clinic. The translational scientist might ask a series of questions:

- Were there preclinical biomarkers that did or could have predicted the AE (e.g., decreased albumin)?
- Is the incidence or severity of the AE associated with increasing exposure (Dose, AUC, Cmax, etc.)
- Are there other compounds in the database with a similar structure to the compound of interest? And if so, were there similar pre-clinical and/or clinical results? That is, is the AE something that could have or should have been predictable as a function of the structure of the molecule?
- Are there any other preclinical measurements that seem to be correlated with the AE? Is the occurrence of the AE associated with any other individual or cluster of AEs?

Enough capability to nail the dose response.
The valley of death isn't crossed until one has demonstrated a dose response, and a competitive, well tolerated dose at that. Once the dose response is nailed, the spigot of pharma, venture, and public funding can carry the compound to market and the valley of death is left behind. Nailing the dose response means that a translational solution must support state-of-the-art PK/PD techniques of modeling and simulation, including successful integration of time-concentration datasets with 'omics and other data.

Fig. 3 Examples of Data that Needs Sharing to Optimize Translational Science



Mark Hovde is Senior Vice President of Corporate Marketing and Business Development for Certara. Certara focuses on reducing the barriers between the phases of research to speed discoveries in chemistry and enables pharmaceutical and biotechnology companies to achieve significant and enduring improvements in the development and use of therapeutic products. Certara owns Tripos and Pharsight.
Tripos provides software for molecular discovery. Pharsight provides PK/PD software and scientific services to improve productivity and decision-making in clinical drug development.

Support of translational workflows. Translational science is much more than analysis of usually disparate datasets. After finding a new relationship or piece of knowledge, the translational scientist will likely need further information to turn her knowledge into progress. Examples might include, "Who else in my company has worked on projects similar to the one in question?" "Do we have the reagents on hand to synthesize this molecule?" "When can I schedule a synthesis of this compound for further testing?" Solutions for translational science must support key workflows as well if they are to deliver improved productivity.

Prospects

To summarize, the translational science imperative is to improve prediction of the efficacy and safety attributes of a therapeutic agent as early as possible. To do so, organizations must jointly improve discovery, preclinical and clinical experimental methods and materials, and allow for graceful integration and joint analysis of discovery, preclinical and clinical data.

Integration of data across the organizational silos of pharma R&D has proven to be a major rate-limiting step for most companies. The extent to which translational approaches may reduce attrition rates remains to be determined and is likely to vary by therapeutic area and class of therapeutic agent. Long-term success will also be predicated on development of better experimental methods and techniques to probe and measure the *in-vitro* and *in-vivo* attributes of candidate therapeutic agents. Translational solutions must be economical to install and operate, and should leverage data storage systems (e.g., cheminformatics, bioinformatics) already present in the enterprise. They should permit graceful integration of datasets across the silos of R&D, with flexible and easy-to-use query engines that require no special expertise to operate. Most critically, a successful solution must support modeling and simulation of the dose response so that the demonstration of competitive response is accomplished as early and economically as possible. With these capabilities, translational science may indeed be a bridge across the valley of death.

■ **mark.hovde@certara.com**

1 Mikael Dolsten, M.D., PhD
2 Pharsight customer survey
3 http://www.fda.gov/oc/initiatives/criticalpath/projects2008.pdf
4 Certara, parent of Tripos, a molecular modeling and discovery IT company, and Pharsight, the leader in PK/PD software.