BY DENISE MYSHKO

EARLY RESEARCH

The Future of INNOVATION

Discovery and research technologies **ARE ADVANCING AND WILL HAVE A TREMENDOUS IMPACT** on the pipelines of the future.

The way new medicines are discovered is on the cusp of revolutionary change. Advances in the understanding of the body at the molecular level and of the diseases that affect people are likely to have a tremendous impact on the development of new medicines.

Experts say bioinformatics and predictive technologies will have the greatest impact, enabling researchers to test and simulate the effects of drugs and biologics on specific targets before the first dose in humans. In fact, analysts from PricewaterhouseCoopers (PWC) predict that by 2020, virtual cells, organs, and animals will be widely used in pharmaceutical research.

"There continue to be significant investments in the field of regenerative medicine, from Pfizer to the U.S. military," says Steven Nichtberger, M.D., president and CEO of Tengion. "Within the next five years, it is possible that patients could receive bioengineered organs built from their own cells that harness the body's ability to regenerate instead of repair."

According to experts at PWC, over the next decade, researchers must gain a much better understanding of the biology of disease. Pharmaceutical companies will need to build a portfolio of products that demonstrate value within the healthcare continuum, use new technology to better manage and share information, and change their cultures to reward true innovation. These changes will have to occur in early and clinical research. The future of drug development will be about the ability to deliver the right drug to the right person at the right time and in the right dose.

Pfizer is one company that has already begun to make those changes.

"We have made substantial investments in computational medicine, the use of powerful tools that allow us to bring together genetic, preclinical, and clinical data to better understand the underlying disease mechanism in a systems biology approach," says Martin Mackay, Ph.D., president, Pfizer Global Research and Development. "We have other tools that enable us to perform complex modeling and simulation analyses of clinical-trial data — not just our own but those in the public domain — to better predict the likelihood of a successful outcome of a particular clinical-trial design before the investment decision is made. We call this enhanced quantitative drug development, or EQDD."

Diana Faulds, director of global content creation at Wolters Kluwer Health, says biomark-

VITAL FEATURES FOR RESEARCH

- A comprehensive understanding of how the human body works at the molecular level.
- A much better grasp of the pathophysiology of disease — the functional changes associated with, or arising from, disease or injury.
- Greater use of new technologies to "virtualize" the research process and accelerate clinical development.
- Greater collaboration between the industry, academia, the regulators, governments, and healthcare providers.

Source: PricewaterhouseCoopers, New York.
For more information, visit pwc.com/pharma.

EXPERTS

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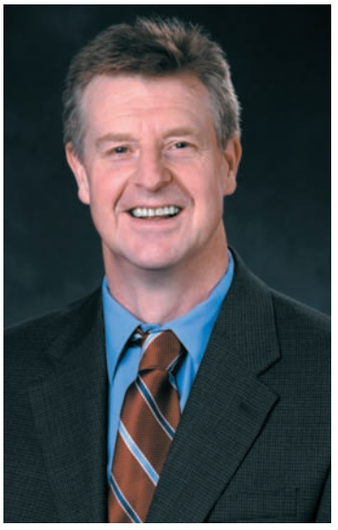
BILLE-JO (BJ) KERNS. VP, Strategic Marketing

Dr. John Secrist
Southern Research Institute

The proper development and implementation of a variety of collaborative arrangements, especially at the early stages of preclinical discovery, will continue to be of increasing importance.

er-based strategies will increasingly direct the approach to discovery, research and development, and market positioning of pharmaceutical and biotechnology agents.

"The identification of meaningful markers that inform clinical decision-making has proven a significant challenge," she says. "Underlying changes associated with a disease are often multifactorial and occur in many diseases, for example diabetes. Distinct biological conditions may present with similar clinical symptoms. Thus, it seems that for many disorders testing will be complex, with multigenetic screening assessment



Dr. Martin Mackay
Pfizer Global Research and Development

By combining the information from different clinical trials we can increase the level of confidence in our decision-making, optimize the design of clinical trials, and actually avoid conducting clinical trials that are not likely to be successful.

based on probabilities of association. New techniques to characterize diseases such as gene expression profiling, genomewide association studies, and the identification of genomic signatures will require powerful bioinformatics support to enable accurate risk prediction. This will require alignment of data management and analysis methods to mine molecular, epidemiologic, and clinical-data sets to maximize value."

Similarly, Douglas Burkett, Ph.D., president of Champion Biotechnology, says over the next several years, cancer is likely to demand an unprecedented approach to personalized disease evaluation and treatment.

"Traditionally, patients are given a drug or combination of drugs according to guidelines or standards of care that, in the oncologist's best judgment, is most likely to work based on the results of clinical studies in patients with similar tumor types," Dr. Burkett says. "In practice, cancer patients often require several courses of drugs and regimens sequentially, which may be ineffective or poorly tolerated, before identifying the optimal therapy. In the meantime, precious time is lost, and patients suffer unpleasant side effects and declining ability to tolerate additional therapy while tumors may continue to grow and mutate and become resistant to therapies, further reducing the future effectiveness of additional anticancer agents. Current cancer drugs are also increasingly expensive. When patients undergo several courses of therapy that are essentially ineffective against their specific cancer, the cost of therapy increases unnecessarily."

Ms. Faulds says the lack of well-validated biomarkers has slowed the development of the companion diagnostics essential for the effective implementation of markers as part of patient management.

"There are three likely approaches emerging: acquisition of specialist diagnostic companies by big pharma, as we have seen with Roche, or partnerships with companies offering companion diagnostics as specialist services are established as options," she says. "Eventually we may also see the basic-science approach applied to point of care with the development of cartridge multivariate assay systems.

Ms. Faulds suggests the development of markers that track clinically relevant changes is potentially a multibillion-dollar market that will reward those companies willing to make a strategic investment.

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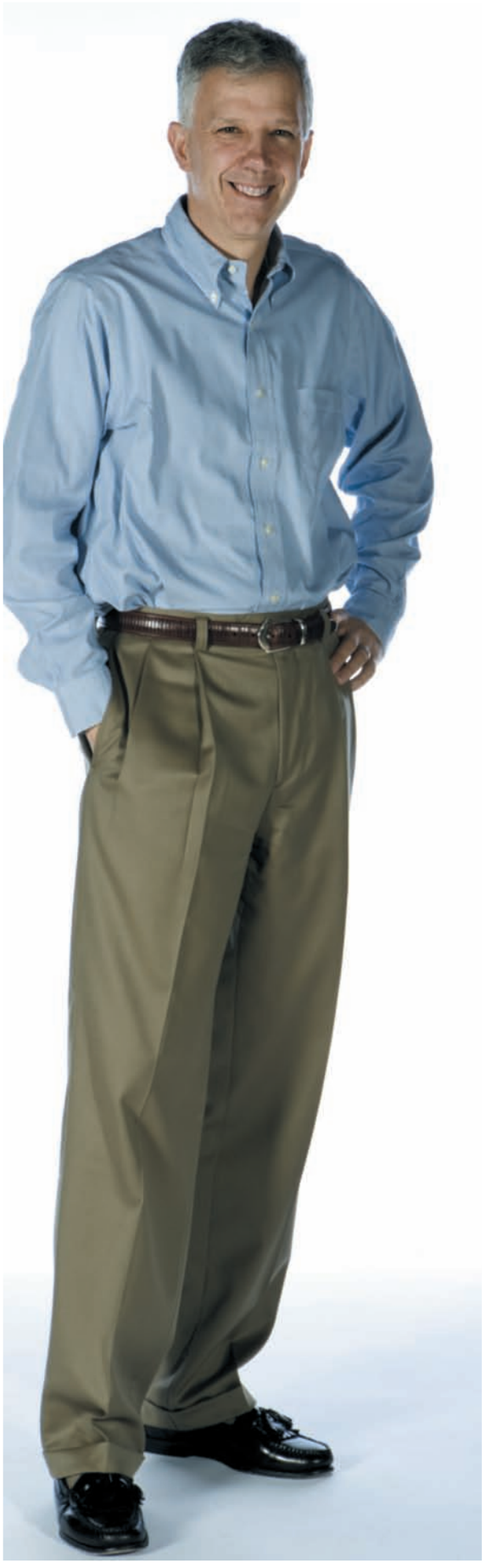
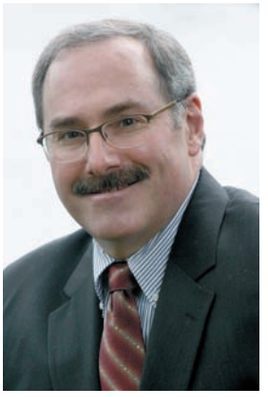


Dr. Lee Babiss *Roche*

We will see that the throughput, quality, and costs of genomic technologies will improve. I am hopeful that we will be able to derive technologies that will allow us to assess biomarkers that are non- or minimally invasive for many diseases.



Peter Lanciano *Neotropix*

Outsourcing will become ubiquitous and strategically focused not only on tasks but fields of study so as to leverage institutional knowledge, therefore enabling virtual research and development teams to be more impactful.

"It may also herald an increased focus on preemptive healthcare, with earlier detection and more specific treatment of disease before the emergence of clinical symptoms," she says. "It will drive more targeted and cost-effective development of clinically differentiated medicines with potential safety, efficacy, and cost-effectiveness advantages. While there will be legal and ethical issues, this approach can also provide a more compelling argument for approval to regulators and to third-party reimbursement decision-makers once a product gets to market."

Bille-Jo (BJ) Kerns, VP, strategic marketing and business development at High Throughput Genomics (HTG), says the ability to screen whole pathways with high precision has become increasingly important.

"Technologies will enable the performance of multiplexed analysis in the early stages of the drug-discovery process as critical to addressing the complex, multifactorial biologic behavior of disease," she says. "Analyzing multiple gene signatures during the initial compound screening process expedites the discovery and development process. The basic biology of the drug-disease and drug-host interactions can be understood and modified earlier in the development process."

Large pharma companies will experience the loss of an unprecedented number of drugs moving off patent in the next few years.

"With the loss of these revenues, we believe there will be even greater movement toward efficiency and streamlining the discovery and development processes," Ms. Kerns says. "Technologies that can be rapidly scaled up and down for maximum flexibility will be paramount."

John Secrist, III, Ph.D., president and CEO of Southern Research Institute, says early-stage research is important for generating clinical candidates at a sufficient rate.

"Acceptable financial models for supporting early-stage research are difficult to find among VC organizations," he says. "At a time when the NIH budget is flat and some pharma organizations are trimming staff, early-stage funding will be a big challenge. A lack of sufficient support at the early stages will have the clear result of reducing the size of pipelines in the future."

Peter Lanciano, CEO of Neotropix, contends that focused research teams of five to 10 people, who can take a concept into the clinic with less than $10 million to $15 million in funding by leveraging collaborative research resources, will drive new innovation because of quick, efficient translational research.

OPPORTUNITIES FOR BIOMARKERS

PWC analysts believe that semantic technology is the new technology that will make it possible to "move" across data sets. Semantic technologies will enable the industry to link clinical-trial data with epidemiological and early-research data, identify any significant patterns, and use that information to modify the course of its studies without compromising statistical validity. In addition, centralized virtual laboratories and the creation of common formats for collecting and reporting biological data will be key for scientists, pharmaceutical companies, contract research organizations, trial investors, and regulators to exchange clinical data and move from one database to another.

Ms. Faulds says the use of appropriate biomarkers will improve efficiency of target and lead compound selection, proof-of-concept studies, and toxicology studies.

"For example, the recent joint submission to the FDA and EMEA of a seven-biomarker panel for assessment of renal toxicity by the Predictive Safety Testing Consortium points to the way forward," she says. "This panel of tests is more sensitive than current standard tests, detecting cel-

Dr. Joseph Amprey *MedImmune*

The global economic crisis will likely yield favorable in-licensing opportunities.

lular damage within hours vs. one week and also indicating which parts of the kidney are impacted. Biomarkers will also support decision-making during clinical development, informing patient selection and stratification studies."

The Predictive Safety Testing Public/Private Consortium was established as a collaboration of industry, academia, and government to identify and clinically qualify safety biomarkers. The consortium intends to provide a venue whereby companies can share and clinically qualify their biomarkers cooperatively.

Lee Babiss, Ph.D., global head of pharma research at Roche, says companies are not investing enough internally and externally to fully understand the molecular basis of the diseases they are studying.

"This has been a big impact on our ability to select the best disease targets for therapeutic intervention and the creation of target, mechanistic, pathway, and disease biomarkers," he says. "The technologies we have in place today provide us with the full capabilities we need to test personalized healthcare concepts preclinically and in the clinic. Regarding the latter, we believe we are particularly well-placed to conduct such studies due to our internal diagnostic capabilities. In the coming years, I believe that the throughput, quality, and costs of these technologies will improve. I am hopeful that we will be able to derive technologies that will allow us to assess biomarkers for many diseases that are non- or minimally invasive. I also believe the industry will begin to apply more imaging work preclinically to help drive lead optimization efforts."

Dr. Steven Nichtberger *Tengion*

There continue to be significant investments in the field of regenerative medicine.

Roche is expected to begin to realize results stemming from some of the new programs that were put in place 18 months ago by the company's Disease Biology Areas.

At Pfizer, the vast majority of new medicines in early-phase research are first tested against one or more biological markers to confirm they act on the underlying mechanism before proceeding to large-scale Phase II trials, Dr. Mackay says.

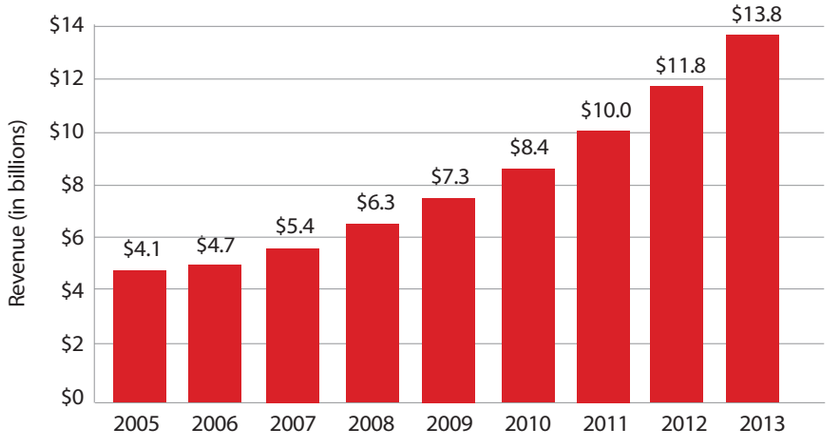
"From an organizational perspective, we have created a Molecular Medicine group comprised of more than 70 top-class scientists who work across the research and development continuum to ensure the systematic application of these approaches," he says. "We continuously look for genetic and other markers that will enable us to understand the differences between patients that will better predict their potential response to therapy. This is facilitated by the fact that we have a 'biobank' containing samples of DNA, blood, and other tissues from more than 100,000 patients, which we have collected from hundreds of clinical trials over recent years and can match in anonymized fashion with the subject's clinical-trial data to analyze response patterns."

The impact of using biomarkers, Ms. Kerns says, will carry through to the market, where better targeting of therapies through biomarkers should reduce the use of ineffective or unnecessary treatments in patients, thus improving cost-effectiveness.

The changing reimbursement environment makes this even more important. PWC analysts note that a growing number of healthcare payers are measuring pharmacoeconomic performance of medicines. As a result, pharma companies will have to prove that their medicines really work, provide value for money, and are better than available alternatives.

"As payers exert their leverage with what is reimbursed — tying drugs more to competitive clinical efficacy advantages — the pharma industry will have to find more efficient ways of determining through R&D what programs will likely succeed," says Joseph Amprey, M.D., Ph.D., senior managing director of MedImmune Ventures. "Consequently, identifying better tools, whether in preclinical development

GLOBAL DRUG-DISCOVERY OUTSOURCING MARKET 2005-2013



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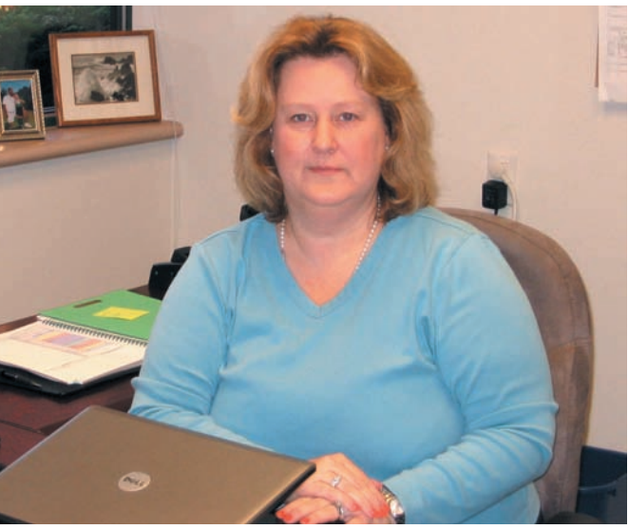

BJ Kearns *High Throughput Genomics*

Analyzing multiple gene signatures during the initial compound screening process expedites the discovery and development process.

through animal models or biomarkers that can be used in early-clinical development will be key to maintaining and growing the top line as well as the bottom line and, most importantly, providing better healthcare."

OUTSOURCING EARLY RESEARCH

To widen the bottleneck in discovery and to keep pace with advances in genomics, combinatorial chemistry, and high throughput screening, bio/pharma companies have begun outsourcing some of their early-research programs.

"Outsourcing will become ubiquitous and strategically focused not only on tasks but for specific fields of study so as to leverage institutional knowledge, therefore enabling virtual research and development teams to be more impactful and plugged in to the overall development process," Mr. Lanciano says. "Big one-stop shops are too inefficient to be effective to biotech and focused pharma companies, as specialization is required."

Contract drug discovery is a high-growth industry. The global drug discovery market reached $5.4 billion in 2007, which increased 15% from $4.1 billion in 2006, according to Kalorama Information. This market is expected to experience robust growth to exceed $8 billion in 2010. The global drug discovery outsourcing market is expected to reach almost $14 billion in 2013.

Dr. Babiss says in the future pharma will be able to decide which technologies need to be internal and whether they should be centralized or available in discovery labs around the world.

"In addition, much of the 'omics' types of technologies are becoming a commodity and many CROs do this work extremely well," he says. "For the biotechs, they will more likely work with CROs to drive their personal healthcare studies, and new biotech companies are being created that will develop the next-generation technologies."

Dr. Secrist says organizations, both large and small, are gradually realizing that it is possible to efficiently and cost-effectively move drug candidates forward mainly using outsourcing partners of various types.

"They are even finding that outsourcing research efforts to the right organizations, as long as the collaborative arrangements are done properly and the teams interact well, is a very effective way to develop new drug candidates," he says. "When these arrangements involve intellectual input from both sides, the results can be very impressive."

PWC experts state that outsourcing partners have played a key role in research and development over the years and will continue to do so. The industry will require their partners to bring not just capacity to handle overflow, but new drug discovery and development technologies, unique skill sets, capacity in low cost regions, etc. An outsourcing partner may have a particular skill set in conducting clinical trials using an adaptive clinical-trial design. The change and opportunities for the partners of pharma are just as large as the change and opportunities in pharmaceutical companies themselves.

Dr. Secrist says outsourcing partners that contribute intellectually to early-stage research efforts should be sought and brought into collaborations.

"The IP sharing involved is a modest consideration when compared with the overall value that could be added," he says. "We have had several such arrangements, and they have been very successful. The continuing use of outsourcing partners, such as companies in India and China, is sensible given the price differential, though the gap is closing. These countries have well-trained and talented scientists who can be of clear value if the interface is managed properly."

He suggests companies need to focus on incentives to their collaboration partners and should also consider specific rewards to internal scientists instrumental in these collaborations.

"Often scientists have a tendency to push their own contributions to a collaboration to get credit when perhaps a more objective view of the external contributions would be of greater value," Dr. Secrist says. "Providing the right incentives should eliminate this obstacle to efficient drug development."

Dr. Amprey says pharma will have to continue to search for a balance between internal R&D and externalization, in-licensing, and M&A.

"Companies will have to evaluate their internal resources with a critical eye in 2009 and beyond and compare these to external opportunities because of the pressures of aging IP portfolios on mature marketed drugs with limited capacity to shore up the ongoing decline from internal pipeline programs," he says. "Pharma should realize more opportunities because of the global economic crisis that will likely yield favorable in-licensing opportunities because of the limited access of public-market capital for mature private biotech companies favoring corporate VC opportunities. Pharma will have to rationalize and be more critical of what can be done more efficiently externally versus internally." ✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

OUTSOURCING IN DRUG DISCOVERY

MAJOR TRENDS THAT HAVE LED TO AN INCREASE IN DEMAND FOR CONTRACT SERVICES IN DRUG DISCOVERY INCLUDE:

- Development of new technologies that continue to increase the number of targets and accelerate the identification of active compounds.
- Pressure to develop new lead compounds as a result of the near-term loss of patent protection for many drug products.
- Increased pressure to reduce the time spent in drug discovery and to bring drugs to market sooner.
- Increased focus on converting fixed costs to variable costs and streamlining operations by contracting for research and development services.
- Heightened regulatory environment and increased complexity has made the internal management of complicated discovery projects more difficult and costly.
- Biotechnology and emerging pharmaceutical companies, in many cases, lack the required in-house drug discovery and development expertise.

Source: Kalorama Information, New York. For more information, visit kaloramainformation.com.

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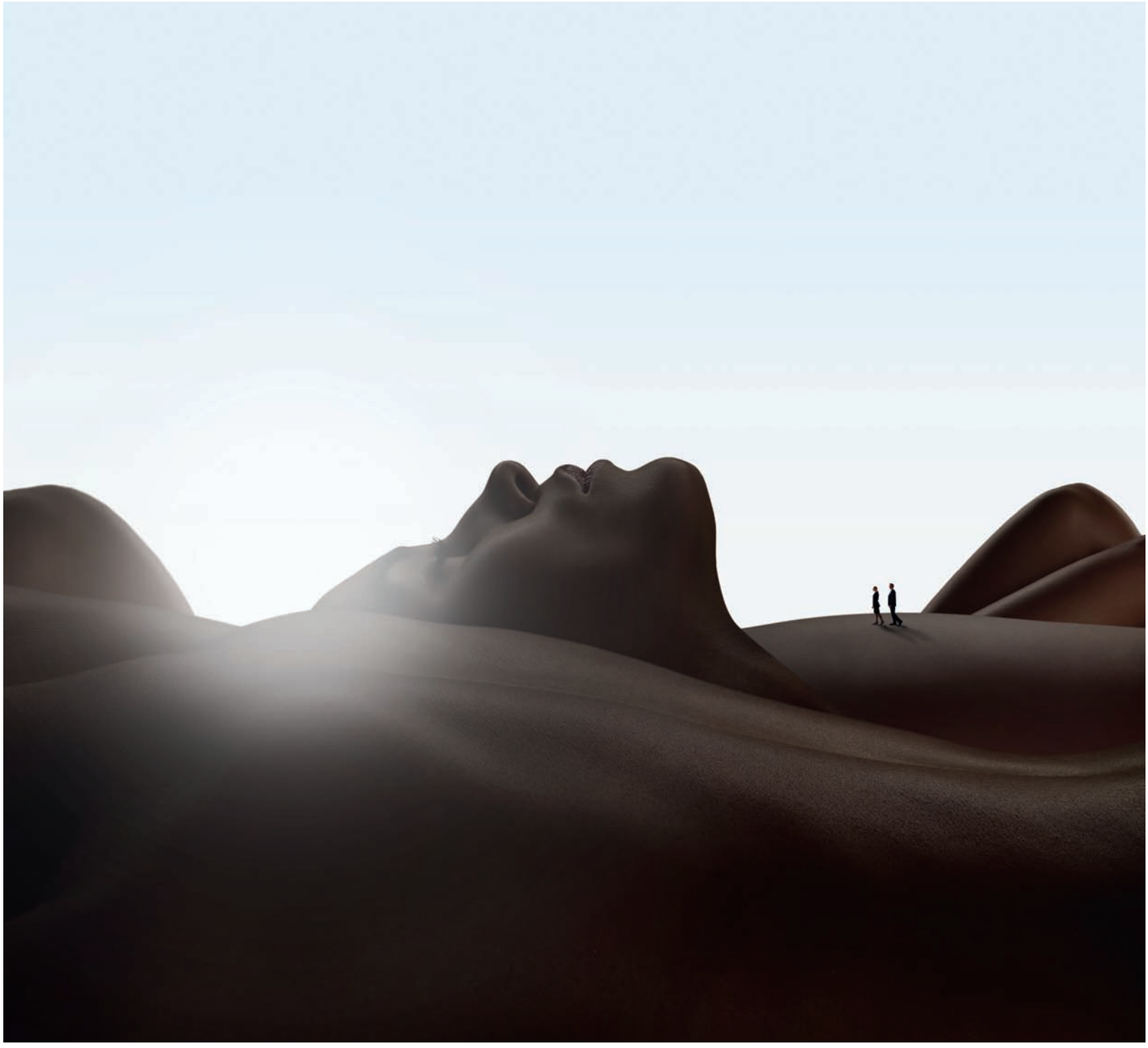

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