maceutical companies are doing already," says Austin. Instead, the initiative will "validate new targets, and even perhaps supply some small molecule compounds, which large or small companies may want to pick up and develop." Noting "screening is the easy part," Austin says the NIH will not do advanced drug development work, except perhaps for certain orphan diseases.

Taking advantage of government and commercial sources, the NIH will build an initial library of 500,000 compounds for screening, all the results of which will enter a public database. The NIH is especially interested in phenotypic screening, in which small molecules are deployed without knowing their biological targets. Drug companies rarely do such screening, because conventional wisdom holds that the targets hit by the small molecules are too hard and time consuming to identify.

But large-scale phenotypic screening is a new and largely untried idea. "Unlike the pharmaceutical industry, which takes [a target, such as] COX2 and only COX2, and then hits it over the head with 500,000 different compounds, we're targeting a biological process," says Craig Crews, professor of pharmacology and chemistry at Yale University (New Haven, CT, USA). Although biological effects of the screens will be unpredictable, they will result in more knowledge about biological mechanisms and structure than a simple 'yes or no' answer to the question, 'did the drug inhibit a single target?'

Such screening "may very well generate a lot of very interesting biological activities, but then the bottleneck will be target identification and followup," says Steve Adams, CSO for NeoGenesis Pharmaceuticals (Cambridge, MA, USA). Adams recommends a broader approach, including affinity-based and functional-based screening against known targets. Crews and Austin are confident that current methods, and new methods in development, will identify individual drug targets.

Although chemical genomics is mainly a research tool, the initiative does put the NIH closer to the drug business, and intellectual property issues remain unresolved. With NIH taking drugs further down the pipeline, public ownership issues will inevitably arise when it comes time to license. Bitter disputes, like those over the anti-HIV treatment AZT and the cancer drug Taxol, where public outrage over exclusive licenses and pricing eventually led to protracted lawsuits involving state and federal governments, could become commonplace. "Problems in the past have arisen when the government has wanted to maintain some level of control over the downstream commercial aspects," says Adams. "The

pharma industry needs, indeed insists, on being able to have control over the development and commercialization process." Austin says any policy decision concerning the licensing of resulting drugs and targets will follow consultation with industry.

The field of chemical genomics only began in 1999, when chemist Stuart Schreiber's group at Harvard University (Cambridge, MA, USA) used a phenotypic screen to identify a novel anticancer drug target, the mitotic kinesin Eg5. Schreiber thus demonstrated that chemical genomics screening could work in academia. "You can see the proliferation of academic small molecule screening facilities around the nation because of that," says

Crews. Cytokinetics (S. San Francisco, CA, USA) has now taken an Eg5 inhibitor into a phase 1 clinical trial.

The new initiative "is a very good idea, because there are certain areas of cell biology that just aren't amenable to, say, traditional genetic analysis," says Crews. "But it will require a large-scale effort, and that's why I think this is quite an appropriate undertaking for NHGRI." Austin acknowledges that a vast new infrastructure will be needed, but doesn't yet know the price tag. "What we're talking about is not cheap," he says. "But there is commitment at the highest level of the NIH to do this. So it will happen."

Ken Garber, Ann Arbor, MI, USA

Public-private partnerships boost research on neglected diseases

The Bill and Melinda Gates Foundation (Seattle, WA, USA) announced on September 21 the availability of \$168 million in grants to fight malaria, including \$100 million earmarked to develop vaccines through the public-private partnership Malaria Vaccine Initiative (Seattle, WA, USA). The charitable sector, by financing early-stage development, has lowered the risk in creating vaccines for diseases prevalent in developing countries. As a result, targeting neglected diseases has now become attractive to biotech companies that are willing to explore new markets.

Creating vaccines for developing countries has not traditionally attracted small biotech companies that typically require high-price markets in order to recoup R&D costs. Recent donations from charitable organizations, such as the Gates Foundation (endowed with \$25 billion), have changed the landscape of drug development, and not only for malaria. "Charities have created a vaccine market specialized in diseases from developing countries such as tuberculosis and malaria. These diseases have, up until now, been overlooked by the industry as a potential

Table 1 Select biotech companies involved in public-private partnerships

Company	Public-private partner	Disease
Apovia (Martinsried, Germany)	Medicine for Malaria Venture (MMV; Geneva)	Malaria
Bayer (Leverkusen, Germany)	MMV	Malaria
Celera (Rockville, MD, USA)	Institute for OneWorld Health (San Francisco)	Chagas disease
Chiron (Emeryville, CA, USA)	Global Alliance for Tuberculosis drug Development (New York)	Tuberculosis
Corixa (Seattle, WA, USA)	Infectious Disease Research Institute (Seattle, WA, USA)	Leishmaniasis
GlaxoSmithKline (London)	MMV	Malaria
Sequella (Rockville, MD, USA)	Aeres Foundation (Rockville, MD, USA)	Tuberculosis
Targeted Genetics (Seattle, WA, USA)	International AIDS Vaccine Initiative (IAVI; New York)	Human Immunodeficiency Virus (HIV)
Therion Biologics (Cambridge, MA)	IAVI	HIV
Berna Biotech (Berne, Switzerland)	IAVI	HIV

Sources: The Initiative on Public-Private Partnerships for Health (Geneva, Switzerland) and company web sites.

market,” says Jaap Goudsmit, CSO at vaccine company Crucell (Leiden, The Netherlands).

Third-party funding has helped bridge the development gap between fundamental research in neglected diseases and its industrial application through public-private partnerships that associate nonprofit organizations, governments and industry (see Table 1).

“Gates has taken a lot of the risk from product development by putting money in interim development,” says Carol Nacy, CEO of Sequella (Rockville, MD, USA), a company specializing in tuberculosis. Sequella works in parallel with the Aeres Foundation (Rockville, MD, USA), a private group that identifies potential tuberculosis drugs from basic research funded by the National Institutes of Health. It then performs proof of principle experiments in humans, going as far as phase 2 efficacy studies, in order to make the product appealing to potential biotech and pharma partners.

As a result, biotech and pharmaceutical companies are more likely to take over development of such vaccines at these later stages, whereas they would not have during the early, riskiest stage of development. “We’re prepared to take greater risks because it is not our shareholder’s money,” says Jeffrey Almond, senior vice president of discovery research and external research and development at Aventis Pasteur (Lyons, France), which is developing a dengue vaccine with Acambis (Cambridge, UK) by adapting the biotech firm’s existing yellow fever technology.

But a few partnerships have discovered some intellectual property (IP) roadblocks when attempting to fill the development gap for vaccines that target the developing world. Drug development for most indications requires some IP consolidation, and companies are generally happy to foot the bill in courtrooms when there is a large market at stake. “Because there is little market value for IP on malaria antigens, patenting them can actually hinder rather than promote innovation,” says Melinda Moree, director of MVI.

Successes in developing a vaccine technology for neglected diseases can have further benefits, in addition to the positive publicity that such an achievement would generate. “Third-party funding helps us validate our technology,” says Vijay Samant, CEO of Vical (San Diego, CA, USA), which has used its plasmid DNA vaccine technology to do research for a malaria vaccine backed by US Navy funding. Once validated, the technology might be applied to vaccines for lucrative markets.

For companies targeting niche markets, there are a number of opportunities in the developing world. “The SARS epidemic has been a catalyst in generating interest for the prevention of other diseases such as influenza, or flu,” says Gurinder Shahi, CEO of life science consultancy Bioenterprise Asia (Singapore). Indeed, “a flu vaccine market is emerging because of SARS,” agrees Goudsmit. He believes that only by vaccinating people against flu will it be possible to distinguish people affected by SARS, because both conditions have similar symptoms at an early stage of the disease. Although governments may foot the bill for a flu vaccine as a preventative measure, middle-income private markets also constitute an untapped opportunity in Asia, says Shahi.

But companies can also make profits by adapting vaccines to the needs of developed

countries. Indeed, the emergence in developed countries of diseases from developing countries has generated dual markets that, until now, existed only for travelers’ vaccines, such as diarrhea and yellow fever vaccines. For example, companies such as Crucell, Bavarian Nordic (Copenhagen) and Acambis are currently focusing on vaccines against the West Nile virus, and SARS has attracted a number of vaccine players (*Nat. Biotechnol.* 21, 720, 2003) as such diseases become an economic burden to countries affected. In addition, the US BioShield proposal now pending before Congress would, if enacted, pony up \$6 billion in public funds to address infectious diseases, such as Ebola, that are now considered security issues (*Nat. Biotechnol.* 21, 216, 2003).

Sabine Louët, London

Concerns raised over declining anti-infectives R&D

In mid-September, officials at the US Food and Drug Administration (FDA; Rockville, MD, USA) approved daptomycin (Cubicin, previously Cidecin) for clinical treatment of skin infections—a seeming renaissance because it is the first time in decades that a product belonging to a new class of antibiotics gained approval. Yet, FDA officials point to a distinct trend toward fewer anti-infective agents being approved per year over the past 20-year period. Thus, even while Cubist Pharmaceuticals (Lexington, MA, USA) is celebrating success with Cubicin, a cyclic lipopeptide, many other would-be developers of anti-infective products at biotech and pharma companies are sounding gloomy about near-term prospects within this market sector.

Moreover, despite resurgent federal interest and support for developing such products for bio-defense purposes (*Nat. Biotechnol.* 21, 469, 2003), continuing uncertainties about the BioShield proposal and more recent concerns about the regulation of federal Small Business Innovation Research grants are adding to the gloomy mood (*Bioentrepreneur*; 4 September 2003, doi:10.1038/bioent765). With venture capital sources scarce, interest in this product sector among big pharma, particularly in antibacterial agents, is “evaporating and the sense of bleakness is pervasive,” says Deborah Nosca of Nereus Pharmaceuticals (San Diego, CA, USA), which is seeking to develop anti-infective products.

Gram-positive skin infections can now be treated with Cubicin (daptomycin), which is the first of a new class of antibiotics to be approved by the FDA in over two decades.

“A large number of pharmaceutical companies—and many biotech companies—have exited the field or reduced their efforts, especially for antibacterials,” says Steven Projan of Wyeth Research (Cambridge, MA, USA), one of several industry representatives who addressed these issues during the Interscience Conference on Antimicrobial Agents and Chemotherapy, convened during mid-September in Chicago. “And when big pharma sneeze, biotech companies get pneumonia and