

As investors favor oncology and rare disease, work in prevalent chronic disease takes backseat

By Jennifer Boggs, Managing Editor

PHILADELPHIA – Compared to oncology, chronic diseases such as cardiovascular disease, diabetes and dementia represent much more substantial costs to the overall U.S. health care system, yet investment and R&D innovation in those areas has been on a steady decline over the past decade or so, according to research compiled by the Biotechnology Innovation Organization (BIO).

Kicking off a series of sessions Wednesday focusing on those highly prevalent chronic diseases, BIO's David Thomas, vice president of industry research, presented some sobering statistics gathered from venture capital studies looking at money going into different disease areas.

According to BIO's most recent research, between 2008 and 2017 U.S. venture capital investment in oncology totaled nearly \$12 billion, while the costs to society in the U.S. were nearly \$125 billion. By contrast, chronic diseases such as diabetes, cardiovascular, dementia and psychiatric disorders racked up much higher costs to society while venture investments for each group came in below \$2 billion. The biggest disparity was seen in the dementia space, which showed less than \$1 billion in venture investment over the course of the decade while direct U.S. health care costs topped \$175 billion.

Similar metrics emerged in terms of disease prevalence vs. venture investment. During the 10-year period between 2007 and 2016, oncology patients numbered between 10 million and 20 million in the U.S. Cardiovascular disease affected more than 50 million people over the same period.

More concerning, noted Thomas, is the downward trends in those chronic disease areas in terms of innovation and R&D on a year-by-year basis.

In terms of development, the field of depression, for example, saw a 50% drop in phase I trial starts for new drugs, as did the type 2 diabetes space. And both the number of new chemical entities approved by the FDA for highly prevalent chronic diseases and the number of unique mechanisms also lagged behind oncology. While the overall industry success is roughly 10% – success defined by programs starting phase I getting all the way to FDA approval – an even lower rate has plagued drugs for prevalent chronic diseases. Based on BIO's data, the chance for FDA approvals of new drugs for depression and type 2 diabetes is 5% each; for pain drugs, the odds are 2%; and for obesity, it's 1%. Drugs targeting addiction and Alzheimer's

aren't even on the board with a 0% chance of FDA approval.

BIO has been periodically publishing reports looking at each of the areas it has designated as a highly prevalent chronic disease, with the most recent report coming out last month focused on Alzheimer's, showing the venture capital funding of U.S. companies with lead programs targeting Alzheimer's was 16 times lower than oncology funding.

Thomas noted the lack of investment and innovation can be attributed to the science on one side – a lack of biomarkers for early disease progression, nonpredictive animal models, the large trial sizes and outcome studies required and the complex disease biology itself – and to market access on the other side – the challenging reimbursement landscape, the generic market and competition plus higher standard-of-care hurdles. All that combines to create a less-than-palatable opportunity for investors, despite the huge unmet health care needs.

'We've had oncology envy'

BIO's findings were unsurprising to panel members, including Ken Moch, president and CEO of Pittsburgh-based Cognition Therapeutics Inc., an Alzheimer's disease-focused firm that has relied on impact and angel investors and NIH funding to date rather than traditional venture capital. In Alzheimer's especially, the late-stage failure rate has sent many VCs fleeing. After all, "if you're probability of success is zero, how do you invest in that?" Moch asked.

Oncology, on the other hand, has become increasingly attractive over the last several years, as it's gone from being viewed to one large indication to a series of rare diseases, offering "bite-sized" and easily manageable disease groups, Moch said. The large chronic diseases can't be divided into easily digestible subsets – at least not with current scientific understanding – so testing requires larger patient populations to test often-subjective endpoints, raising the risk of expensive failures.

For that reason, there's been a "tremendous shift to focus on the rare disease space because, frankly, that's where the economic incentives are," said the FDA's Aliza Thompson, medical officer in the division of Cardiovascular and Renal Products at the Center for Drug Evaluation and Research. A nephrologist by training, with more than a decade at the FDA, Thompson admitted that "we've had oncology envy for a long time."

The FDA has a number of development incentives for rare diseases, and oncology research has gotten a boost from the National Cancer Moonshot initiative; meanwhile, in the postmarketing environment, rare disease therapies have far more success with payers, who remain wary about covering high-cost treatments for common diseases.

“From a public health standpoint, it’s critical we tackle this issue,” Thompson said.

Solutions will have to be multipronged, taking advantage of existing data and investing in the science to really tease out the pathology and figure out key molecular pathways. “We call this a large group of patients when we haven’t adequately set phenotypes to these indications,” Thompson added. If a precision medicine approach can be used, then perhaps patient populations can be segmented – for example, if there was a tool or biomarker to identify high-risk patients, they could be enrolled in a smaller and shorter trial to test efficacy.

Other solutions could involve utilizing real-world evidence and data-gathering, getting more patient-reported outcome data into the hands of physicians, said Divakar Ramakrishnan, vice president and chief digital officer at Eli Lilly and Co. He added that one of the problems with chronic disease treatment is compliance – “by the time of the third refill, only about 20 percent of patients are still on it,” he said.

Finding the unmet need

That compliance issue is particularly acute in the cardiovascular (CV) disease space, where there are a number of products on the market – many of them generic – to address both “actual manifestations as well as effective preventive” treatments, said Eric David Peterson, professor of medicine at Duke Clinical Research Institute, during a follow-up session. The industry has demonstrated that developing CV drugs is possible and there is a well-established – albeit rigorous – regulatory pathway. Yet, about half patients who should be on therapy are not, and “that’s a huge problem,” he added. “Why should new drugs be developed if existing drugs are not being used?”

Sadly, that seems to be the view of many drug developers and investors. As many as one in four deaths in the U.S. can be attributed to CV disease and it is considered the No. 1 cause of death in the country. Yet, a report by Clearview Healthcare

Partners on the state of innovation in the industry found that a mere 1% of therapeutics in development were targeting CV disease, noted John Glasspool, who moderated the CV-focused session. “I’m glad you made it to the 1 percent session,” he told the audience.

Glasspool, who helms Anthos Therapeutics Inc., a company formed earlier this year with a \$250 million investment from Blackstone Life Sciences and an in-licensed antithrombotic agent shelved by Novartis AG, echoed comments raised in the earlier session, citing the fact that an early read of clinical efficacy is nearly impossible in the development of CV drugs, namely because they tend to be more preventive. He also cited the “macro piece,” or the fact that payers have indicated willingness to pay top dollar for rare disease drugs, making them a much more compelling bet for investors. In CV, too, those roadblocks are “compounded by the fact that regulators want to see” large CV trials. (See *BioWorld*, Feb. 28, 2019.)

But addressing all those issues won’t help without filling the gaps between innovation and patients’ needs.

“We’re tasked with finding where the unmet need is,” said David Soergel, global head of cardiometabolic development at Novartis.

One of the difficulties is the fact that targeting CV disease often means treating patients who are asymptomatic. Finding and validating biomarkers and making genetic testing a routine part of patient interaction would help, as would taking advantage of technology to put more control in the hands of patients themselves.

That’s an approach being taken by Incarda Therapeutics Inc., which is testing a drug-device combo designed to deliver an inhaled formulation of well-known drug flecainide to treat recent-onset paroxysmal atrial fibrillation. What sets the product, Inrhythm, apart from existing treatments is that it is being developed for patients to use alongside device-based monitoring that would alert patients to an atrial fibrillation episode. (See *BioWorld*, Feb. 11, 2019.)

If successful, said Incarda CEO Grace Colon, the technology would be useful for the patient, while also providing data to the physician. It would also allow early stage intervention in atrial fibrillation, a progressive disease that currently represents a \$30 billion cost to the U.S. health care system each year. ♦