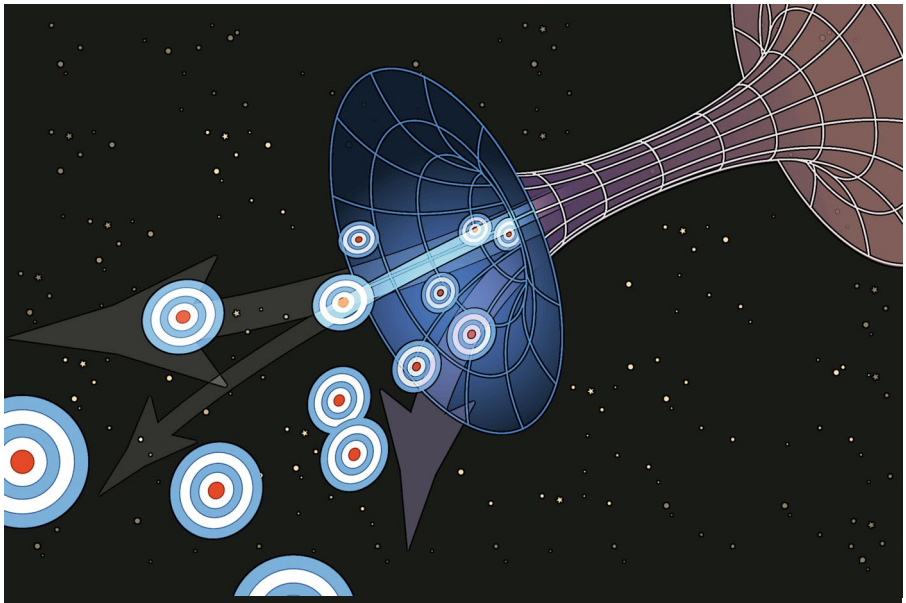

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# Massive NIH–industry project opens portals to target validation

Five years in, the US$360 million Accelerating Medicines Partnership is yielding tools to speed up drug discovery for rheumatoid arthritis, lupus, diabetes, Alzheimer disease and Parkinson disease.

*Elie Dolgin*

In April 2014, Francis Collins stood before a US Congressional committee and touted the creation of an "unprecedented public–private effort" that would use "cutting-edge scientific approaches to sift through a long list of potential therapeutic targets and biomarkers" and ultimately "treat and cure disease faster".

Five years and hundreds of millions of dollars later, the Accelerating Medicines Partnership (AMP) is delivering on that promise, says Collins. Most notably, AMP has created new technology standards for studying the diseased cells responsible for lupus and rheumatoid arthritis (RA), and has produced publicly available resources for analysing the genetic basis of Alzheimer disease and type 2 diabetes.

"Nobody would've said those are easy tasks to achieve in a short period of time, but by working with industry and academia at the same table, focused in this precompetitive space, there's been pretty dramatic progress," Collins, the long-serving director of the NIH, told *Nature Reviews Drug Discovery*. "By any measure, this has lived up to expectations."

One obvious measure is funding — where backers of the public–private partnership have doubled down on the collaboration. AMP's initial budget of US$230 million has jumped to some $360 million, when counting in-kind contributions from the programme's 12 pharmaceutical and non-profit partners (TABLE 1). Although the bulk of the extra cash comes from the NIH, industry allies upped the ante in the RA and lupus effort, and kicked in funds to start up a Parkinson disease AMP project. Each project is now on its own timeline, with funding secured until 2020 or beyond.

"To me, one of the signs of success is if people ask for more of something," says David Wholley, director of research partnerships at the Foundation for the NIH, which manages the programme. Discussions are already ongoing about creating a "sort of AMP 2.0", Wholley says.

Industry insiders cannot yet point to drug candidates that owe their origins to AMP — and researchers who study precompetitive research models say that's to be expected. "It takes a lot of time to get started in such huge consortia," notes Hilde Stevens, of the Institute for Interdisciplinary Innovation in healthcare. Mechanisms of governance need to be built, platforms for knowledge developed and, perhaps most importantly, trust between partners established. "Once the trust is there," Stevens says, "the data will come and the outcomes will be generated."

Already, however, AMP members say the public–private partnership has helped them focus their R&D activities, stopping programmes that seem less biologically relevant, accelerating others and revealing new targets potentially worth pursuing in the future. "I would expect within the next 5 years to see a rapid pace of translation in academia and in industry," says Mikael Dolsten, president of worldwide research and development at Pfizer, who co-chairs AMP's executive committee with Collins. "I think that would have taken two or three times longer if we hadn't built these granular, high-resolution maps of diseases together."

Even companies that are not affiliated with the project are sampling the fruit of AMP's labour. For instance, Aris Baras, head of the Regeneron Genetics Center, says his team now routinely crosschecks internal company findings against an AMP-developed database. "It's one of the few external resources we turn to to get independent results."

## No one mold

The four ongoing AMP projects are united by common goals, but the research agenda of each is distinct. That was by design, says Dolsten, and reflects the state of scientific knowledge in the various disease areas. "We cherry-picked what would be most impactful for each of those diseases," he says. "It's the antithesis of the cookie-cutter approach," adds Wholley.

For the $52 million joint RA and lupus initiative, that meant starting with the basics of procuring, storing and analysing the tissues that are affected by each autoimmune disease. In RA, researchers needed to develop ways to biopsy synovium, the tissue that lines joints — a practice rarely done before AMP outside of Europe. Academic members of the project travelled to the UK to learn the tools of the trade. Six teams each tried different ways of preparing cryopreserved synovial tissue for cell sorting, mass cytometry and single-cell RNA sequencing. The consortium then came up with a consensus protocol that they published last year.

They have also described unique transcriptomic signatures of macrophages, T cells, B cells and fibroblasts associated with the inflammatory process. And using machine-learning algorithms to compare histological features and gene expression data, the researchers identified three distinct synovial subtypes that could explain differences in pain levels experienced by patients with RA. "This is really the first large-scale assessment of rheumatoid arthritis tissue by multiple high-dimensional analyses," says Deepak Rao, a rheumatologist and immunologist at the Brigham and Women's Hospital.

Table 1 | **Accelerating Medicines Partnership funding levels**

| Disease | Industry members | NIH funding | Industry funding | In-kind contributions | Non-profit funding | Total |
|---|---|---|---|---|---|---|
| Alzheimer disease | AbbVie, Biogen, Eli Lilly and GlaxoSmithKline | $162 million | $22.2 million | $40 million | $1 million | $225.2 million |
| Diabetes | Eli Lilly, Janssen, Merck, Pfizer and Sanofi | $31 million | $21.5 million | $6.5 million | $0.3 million | $59.3 million |
| Rheumatoid arthritis and lupus | AbbVie, Bristol-Myers Squibb, Janssen, Merck, Pfizer, Sanofi and Takeda | $24.9 million | $25.5 million | $0 million | $1.2 million | $51.6 million |
| Parkinson disease | Celgene, GlaxoSmithKline, Pfizer, Sanofi and Verily | $12 million | $8 million | $2 million | $2 million | $24 million |

In phase two of the project, the researchers will scale up to repeat the analysis in more subjects — and they are taking a similar approach with kidney tissue from patients with lupus nephritis. According to New York University rheumatologist Jill Buyon, researchers have collected nearly 150 renal biopsies for ultra-sensitive, droplet-based RNA-seq analysis of cryopreserved kidney tissue.

This work has already started to reveal the subpopulations of immune cells that are implicated in disease. But additional samples are still needed to validate the preliminary findings. "What we have now is a good window into what the biological players are," says Pfizer's Marty Hodge, who co-chairs the RA–lupus project's steering committee. "What the next year will bring us is information on how these biological arms correlate to disease activity and treatment responses."

## Entry portals

The $59 million diabetes project revolved more around software than wet-lab work. Within about 18 months of launch, the diabetes team set up an online 'knowledge portal' replete with DNA sequences, functional genomics findings, and epigenomic and clinical data from huge numbers of patients — in an easily searchable and analysable format. "We wanted to empower everybody," says Jose Florez, a diabetes researcher at the Massachusetts General Hospital and the Broad Institute.

At last count the portal combined records on 113 traits from 62 data sets, and it will soon include sequence information from approximately 52,000 complete exomes, around half from patients with diabetes and half from healthy controls. According to Noël Burtt, of the Broad Institute, the portal now receives about 100 visitors per day and has been cited in more than 40 published papers.

One paper that used the portal for independent replication came out last year from Baras's group at Regeneron. Company scientists had previously found that inactivating variants of the *ANGPTL4* gene are associated with lower triglyceride levels and lower risk of coronary artery disease. The diabetes portal helped the team show that these loss-of-function variants are also associated with improved blood sugar regulation and lower rates of diabetes. Although Regeneron's phase III candidate evinacumab targets ANGPTL3 rather than ANGPTL4, both angiopoietin-like proteins inhibit the same enzyme responsible for breaking down triglycerides. As such, says Baras, the genetic findings are transferable across targets and add weight to the therapeutic rationale of blocking this pathway in patients with elevated lipids. "This is validating," he says.

The portal also empowered its architects to run the largest disease-specific exome sequence analysis to date. In that study, Michael Boehnke, a statistical geneticist at the University of Michigan School of Public Health, led a team together with Florez and University of Oxford endocrinologist Mark McCarthy that identified rare variants in 3 genes and in 12 gene sets that could point to potential diabetes drug targets. "We've got some truly interesting findings here, but we need larger samples," Boehnke says, noting that at least twice as many exomes are probably required to account for more of the disease's genetic underpinnings.

In work that remains unpublished — and confidential for now — the same team used the exome data set to validate targets of interest to the project's industry partners. A consultant consolidated the suggested targets into a master catalogue of 200 priority genes in such a way that every company would know what others were working on but not who exactly had asked about which target. The researchers then checked which genes on this 'grey-zone list' were associated with disease burden by looking at factors including glycaemic, renal, hepatic and cardiovascular health.

"The great thing about the AMP diabetes portal is that it's gone well beyond diabetes," says Caroline Fox, head of genetics at Merck.

For example, one as-yet-undisclosed grey-zone gene variant provides protection against diabetes but is associated with an increased risk for another condition. "When you see those types of data that cross disease states, that's extremely informative as it gives you concepts both with respect to efficacy and safety risk as your pursue targets," says Eli Lilly's Melissa Thomas, who co-chairs the diabetes project's steering committee. The group has "talked about" ways of publishing the process, data or findings from the grey-zone exercise, she says.

## Brain trust

The Alzheimer disease branch of AMP produced a knowledge portal of its own that warehouses molecular data collected from around 3,500 human brains and blood samples. Initially, researchers wanting to use the resource had to download the raw data and run analyses off-line — as Ben Readhead, a bioinformatician at Arizona State University, did to identify gene signatures of viral activity in the brains of Alzheimer disease patients.

The portal, says Readhead, "is unparalleled in terms of the breadth and scope and resolution of the data." But it wasn't user-friendly. So last July, Sage Bionetworks unveiled a web-based tool called Agora that allows users to search for genes of interest and their putative links to Alzheimer disease. Agora also highlights 95 candidate genes that academic teams have nominated as potential targets.

A team led by Ben Logsdon and Lara Mangravite, both at Sage, have parsed these data to show that Alzheimer disease-related changes in gene expression fall into five main biological pathways. Three of these — neuroinflammation, endosomal trafficking and RNA splicing — are already under active drug discovery consideration. But the network analysis also revealed the importance of oligodendrocytic function and heat shock responses to protein misfolding, both of which had flown somewhat under the radar in the Alzheimer disease research community.

What's more, notes Logsdon, genes involved in both of these underappreciated processes consistently showed different expression patterns between male and female patients. "It suggests there's a lot of sex-specific biology in Alzheimer's that we've missed," he says. "That has broad implications for personalized medicine and at every stage of the drug development pipeline."

In a companion analysis, neuro-geneticist Joshua Shulman, at Baylor College of Medicine and Texas Children's Hospital, and his colleagues compared Logsdon's findings with gene expression profiles from 96 different mouse models of Alzheimer disease and other neurodegenerative disorders. "There are some clear areas where there are features of Alzheimer disease that are not recapitulated in those models," says Shulman.

This kind of output helps the research community to understand which preclinical models and mechanistic studies will give the best insights into different aspects of Alzheimer disease pathogenesis, he adds. It will also inform which mouse models to develop next. Mice with aberrant unfolded protein responses and oxidative phosphorylation pathways are at the top of the list, he says.

While the target discovery and validation side of the Alzheimer disease project consumed about $64 million of the $225 million allotted for that disease area, the rest of that budget was earmarked to support the ongoing A4 and DIAN-TU prevention trials — with an emphasis on incorporating tau imaging into those studies. Both A4 and DIAN-TU are testing amyloid-β-targeted antibody therapies in at-risk, asymptomatic populations, and part of the AMP funding went towards incorporating tau imaging into those studies. (Earlier plans to fund a third prevention trial and a trial of an immune-stimulating transplant drug were scrapped).

Neurologist and A4 leader Reisa Sperling, at the Brigham and Women's Hospital, says that the AMP funding plus a smaller contribution from the Alzheimer's Association allowed her team to obtain tau-positron emission tomography (PET) scans from nearly 700 trial participants who are cognitively healthy but show amyloid positivity on PET imaging. (AMP helped fund another 244 scans for DIAN-TU.) At baseline, "we see that greater amyloid burden is strongly correlated with greater tau burden in exactly the anatomic distribution that is seen in typical Alzheimer's disease," Sperling says. However, how that pattern changes after treatment with the amyloid blocker solanezumab or a placebo won't be known until 2022, when the A4 data are unblinded.

### And then there were four

The newest AMP arrival on the scene is making rapid progress of its own. Since launching a little more than a year ago, researchers on the $24 million Parkinson disease project have collated whole-genome and transcriptome records from four large cohort studies — consisting of more than 3,000 patients and 1,700 healthy controls — into a knowledge portal. "We're building on a lot of the lessons learned from the other AMPs," says Todd Sherer, CEO of the Michael J. Fox Foundation for Parkinson's Research, which gave $2 million to the project. "That leverage was really important for us," he says.

A beta version of the harmonized data set and portal is set to go online in March 2019. After "kicking the tires" and working out all the bugs, a public release should follow in August, says David Glazer of Verily, which is developing the platform.

Once the portal is up and running, the Parkinson disease project will focus primarily on identifying reliable biomarkers, not drug targets. That's because industry partners cited patient heterogeneity as one of the biggest sources of failure among studies of disease-modifying therapies. "The success of clinical trials aimed at developing new treatments for PD hinges on identifying and validating biomarkers that can track the progression of the disease," says Tanya Fischer, global project head for neurology at Sanofi.

One such failure occurred late last year, when researchers halted a large, phase III trial of inosine, a drug designed to boost levels of the antioxidant urate. An interim analysis showed that inosine was unlikely to slow progression of the disease. In a future stage of the Parkinson disease AMP project, researchers will incorporate data from the inosine study and from an ongoing phase III trial of the calcium channel blocker isradipine into the knowledge portal. They also plan to catalogue the proteomes and possibly the metabolomes of spinal fluid and blood samples collected during the four cohort studies.

If all goes well with biomarker development, industry and academic investigators intend to use those disease indicators as diagnostic aids and tools for patient stratification in future trials, says Marg Sutherland of the NIH's National Institute of Neurological Disorders and Stroke, who co-chaired the steering committee with Fischer before moving to the Chan Zuckerberg Initiative in March. Ultimately, they hope to move on to therapeutic target identification as well.

AMP has also begun to spawn offshoots. In 2017, the NIH and 12 drug companies launched Partnership for Accelerating Cancer Therapies (PACT), a 5-year, $220 million project to validate biomarkers for immunotherapy treatments. Because PACT was funded through the Cancer Moonshot, that research collaboration was never brought under the AMP umbrella. But "it really started out as: can we do an AMP for cancer?" says Wholley.

Discussions are also ongoing around how the NIH and industry can continue to work together to speed up target validation in other disease areas. Just this past February, the AMP leadership approved plans to explore adding a fifth arm dedicated to schizophrenia, an idea that had been on the table at the project's inception but that only began to gain traction among industry partners in recent years.

"We may not be done with AMP projects," says Collins. "There are others swirling around."