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AITIA

Causal artificial intelligence and digital twins are transforming drug discovery and development

Through its patient-data-derived Gemini digital twins, Aitia is uncovering the hidden genetic and molecular mechanisms that causally drive human disease, and accelerating the discovery of breakthrough drugs to improve outcomes for neurodegenerative disorders and cancer.

Aitia predicted the future. More than 25 years ago, the biotech's CEO foresaw how technology would enable researchers to reverse-engineer 'hidden' biological circuitry directly from genomic and molecular data from patient tissue, and radically expand knowledge of the causal molecular mechanisms that drive disease. Estimates are that only ~5% of the biological interactions responsible for human disease are known. Now, after staying true to that mission, Aitia is positioned to realize its vision. The era of artificial intelligence (AI)-powered, hypothesis-free drug discovery and development has arrived.

Boston-based Aitia's approach fundamentally differs from previous methods of drug discovery and from other AI techniques. While technology has become increasingly sophisticated, the current approaches have remained trial-and-error at their core. Aitia CEO and co-founder Colin Hill believes that has to change.

"Really transforming this field and radically speeding up discovery and development requires breaking open the complexity of diseases from the molecular and genetic level up," Hill said. "That's what Aitia is about."

Founding an AI pioneer

Hill became interested in how systems self-organize as a researcher at the Santa Fe Institute in New Mexico and a PhD student in theoretical physics at Cornell University in the 1990s, leading him to study networks in cells and tissues, and create theoretical gene-network models. When Hill learnt about advances in DNA sequencing and gene-expression profiling, he foresaw how this explosion of human molecular data could combine with advances in computing power to facilitate the creation of accurate models of human biology.

"It seemed like it was inevitable," Hill said. "Measurements of 'cancer tissue versus normal tissue' or 'drug treated versus not' were going to give us this panoramic molecular view of what's happening inside diseases."

Hill co-founded GNS Healthcare, now called Aitia, with Iya Khalil (now head of AI and genomics at pharmaceutical giant Merck) in 2000 to realize that vision. As Hill predicted, the cost of sequencing fell quickly, computing power aggressively increased, and AI technology advanced rapidly. Aitia evolved over the years while waiting for the field to generate enough human multiomic data to support its founding mission of treating and curing diseases by discovering underlying biological circuitry.

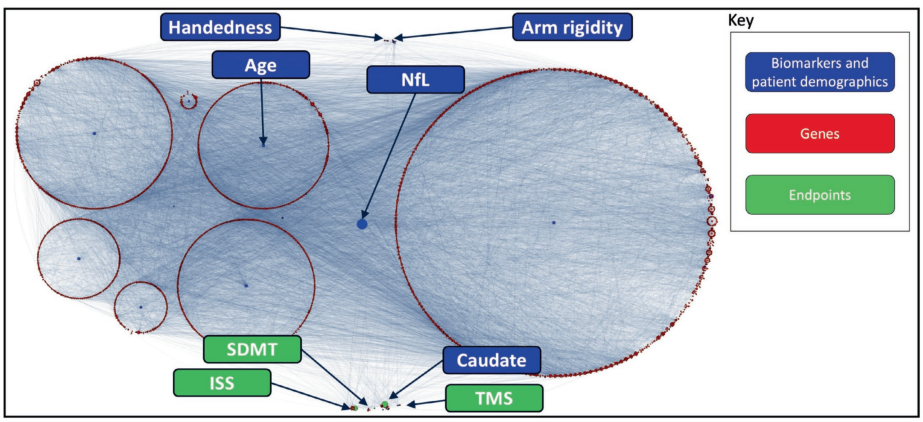

Fig. 1 | Huntington's disease digital twins built on causal AI and human multiomic and clinical data. The digital twin incorporates human multiomic data with motor and cognitive progression outcomes to reconstruct known and unknown mechanisms. The complex, interconnected network has 22,770 nodes and 5,383,791 edges. ISS, integrated staging system; NfL, neurofilament light; SDMT, symbol digit modalities test; SWR, Stroop word reading; TMS, total motor score.

Today, Aitia has the data to execute the work Hill envisaged. The company has established a critical mass of data partnerships in neurodegeneration and oncology. Jeanne Latourelle, senior VP of precision medicine at Aitia, said the company is "very data hungry" and has fed its appetite with over 25 strategic data partnerships.

The partnerships have enabled Aitia to access datasets that include DNA sequence variation, gene expression and/or proteomics data, and quantitative clinical outcomes for thousands of patients. Using causal AI and cloud computing, Aitia is turning the data into Gemini digital twins that reverse-engineer the hidden 95% of human biological circuitry.

> "The era of AI-powered, hypothesis-free drug discovery and development has arrived

Creating Gemini digital twins

Gemini digital twins are computational representations of disease that allow Aitia to conduct billions of virtual experiments based on human biology. The digital twins reverse-engineer the known and previously unknown genetic and molecular interactions that drive clinical outcomes. The causal AI platform goes beyond deep learning and large language models to create increasingly accurate replicas of human disease directly from human multiomic data.

Mainstream AI relies on correlation, asking "is A related to B?" across many dimensions and variables. The causal AI platform tests vast numbers of hypotheses of the form "does A cause B?" versus "does B cause A." Jean-Michel Gries, president and COO at Aitia, explained what that means for drug discovery.

"The technology links everything from the genetics, the gene-expression levels, the proteins, to the clinical endpoints. We are able to state, 'this is what the FDA [US Food and Drug Administration] or the EMA [European Medicines Industry] is expecting as a clinically meaningful impact' and filter out the things that will not give that magnitude of effect. That's very powerful and it's because we have the causality chain," Gries said.

Aitia is using the technology to uncover new biological mechanisms and discover and validate novel drug targets in a radically more powerful and accurate way than was possible before. The digital twins allow for accurate simulation of gene and protein knockdowns at the individual patient level across patient cohorts, enabling the discovery and genetic validation of drug targets and biological mechanisms that would otherwise

remain hidden for decades. Aitia creates drug candidates against these targets and advances them to the clinic.

In addition to discovering novel drug targets faster and more cheaply than wet labs, Aitia's digital twins successfully predict clinical outcomes, enabling their use to design clinical trials. The ability to identify targets with a causal link to disease and predict clinical outcomes could enable Aitia to address one of the industry's most persistent problems.

"We should see less attrition in phase 2 because we see the same causal pathways in our models and in patients. Currently, attrition is in the 60% range in phase 2 alone. Reducing that would be transformative for drug development and patients. That's where we think we're going to be the game changer," Gries said.

Aitia has validated the technology via multiple patient cohorts, in vitro and in vivo experiments, and clinical studies, resulting in over 70 peer-reviewed articles and abstracts in publications including *The Lancet Neurology* and *PLOS One*. Pharmaceutical external research and development (R&D) groups have recognized the power of the platform, leading Aitia to successfully partner with 17 of the top 20 pharma companies.

Evolving to build a pipeline

Aitia previously operated as a provider of AI technology. Over the past two years, the company has evolved and become an AI-powered drug discovery and development organization.

"We were cut off from updates from partners about whether we were right on the money with a target or we missed something. We didn't have a feedback loop to continue learning based on testing of our targets," Gries said. "The idea behind the pivot was to get more feedback and economic value."

John Maraganore, founding CEO of Alnylam, has supported Aitia's transition since becoming chair of the board in 2022. Since then, Aitia has worked to access drug development capabilities while staying as virtual as it can, to make the best use of funding. The company partnered with Charles River Laboratories (CRL) to perform wet-lab validation of novel targets and create and test drug candidates in preclinical systems.

The data Aitia feed back into the platform will come from its own pipeline. The biotech is focusing on neurodegenerative diseases because it has experience and data that could tackle the "huge unmet medical needs, morbidity, and burden of disease," Gries said.

Aitia accessed the data from the prospective observational biomarker study in premanifest and early Huntington's disease, TRACK-HD, after it partnered with the CHDI Foundation to create a computer model of Huntington's (Fig. 1). Using the model, the company identified a novel target that affects cognition and motor function in Huntington's (Fig. 2). The finding is a landmark in AI-enabled drug discovery.

"This is, I believe, the first truly hypothesis-free discovery of human biology that's going to be making its way into the clinic," Hill said. "I don't think the discoveries that have been made by other AI drug discovery companies that have entered the clinic have been truly novel targets, coming directly from the data. I think this represents a real paradigm shift for the industry as well as for the disease."

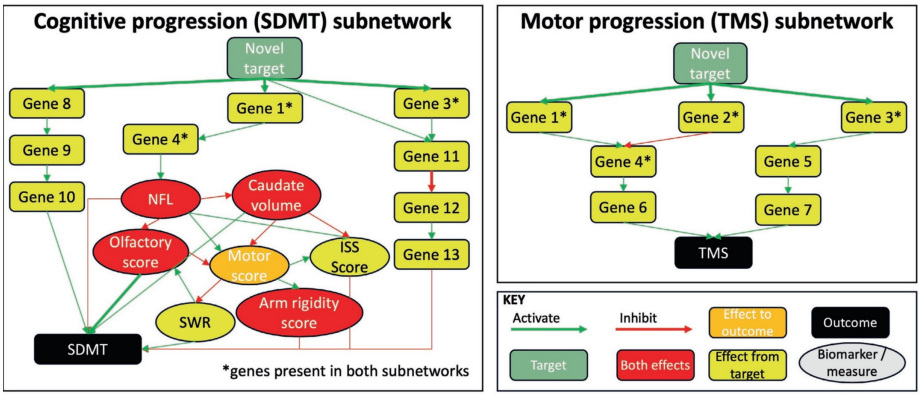

Fig. 2 | Discovery of a novel target impacting cognitive and motor progression from Huntington's disease digital twins. ISS, integrated staging system; NfL, neurofilament light; SDMT, symbol digit modalities test; TMS, total motor score.

Huntington's is one of two programs Aitia plans to take through phase 2 in-house. Aitia plans to file an investigational new drug (IND) application in 2025. The other program is targeting amyotrophic lateral sclerosis (ALS) and is in discovery. While the program is early stage, Gries is encouraged by a large ALS dataset that will enable his team to "dissect virtually what's happening in different areas of the brain."

Aitia also has programs in Alzheimer's and Parkinson's disease that it plans to partner around the IND stage. The biotech has identified novel Alzheimer's targets and shown that drugging them may have a far bigger effect on measures of cognition than previous drugs. However, the size and complexity of Alzheimer's and Parkinson's disease trials means Aitia wants a partner to handle clinical development.

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> Colin Hill,
> CEO & co-founder, Aitia

Partnering the platform

Aitia continues to use its capabilities to support partners in oncology and cardiometabolic diseases. Collaborators typically approach Aitia with one of two requests. Some want to discover novel targets with biological connections to clinical outcomes and create drug candidates. Other partners need to simulate their drug candidates in the digital twins to discover the biomarkers of response and responsive patient populations.

"Where we have the best value for our biopharma partners is in our ability to make connections between biology and clinical outcomes. That's the unique piece that we're able to do," Latourelle said. "We can find novel targets and show if some patients have unique characteristics that interfere with the drug's biological mechanism."

Aitia is applying its skills to pancreatic cancer and Parkinson's in collaboration with Servier. After creating digital twins of the solid tumor from multiple human multiomic data sources, Aitia uses them to find genes that affect clinical outcomes and identify subpopulations that are most likely to respond.

In Parkinson's, Aitia is simulating the mechanism of action of Servier's leucine-rich repeat kinase 2 (LRRK2) inhibitor currently in the clinic. Servier identified the digital twins as a way to find biomarkers that indicate a patient may respond to the therapy.

Aitia has a strategic agreement that allows it to use CRL and Valo's AI-powered Logica in its discovery programs. Logica uses predictive models and other tools to translate targets to candidate nomination. Logica is equipping Aitia to accelerate R&D and has "a very different risk profile compared to starting its own chemistry group," Gries said, "and will allow us to address the three major problems of drug development: having the right target, designing the right drug, and going after the right patient population."

Transforming R&D

After patiently working towards Hill's far-sighted vision for years, Aitia is now rapidly realizing its goal of using causal AI to reverse-engineer biology. The amount and variety of data is increasing quickly, with Latourelle naming single-cell omics as a game changer, and AI and computer capabilities are keeping pace. All the pieces are in place for a transformative effect on R&D.

"The next five to 10 years are going to be amazing with discoveries truly being made in a hypothesis-free way," Hill said. "The complexity of these systems is above and beyond what people really understand. It's not possible to overcome it with just higher-throughput screening. The unraveling of biological complexity needs to happen to make this work. This is what Aitia really leads the industry in."

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