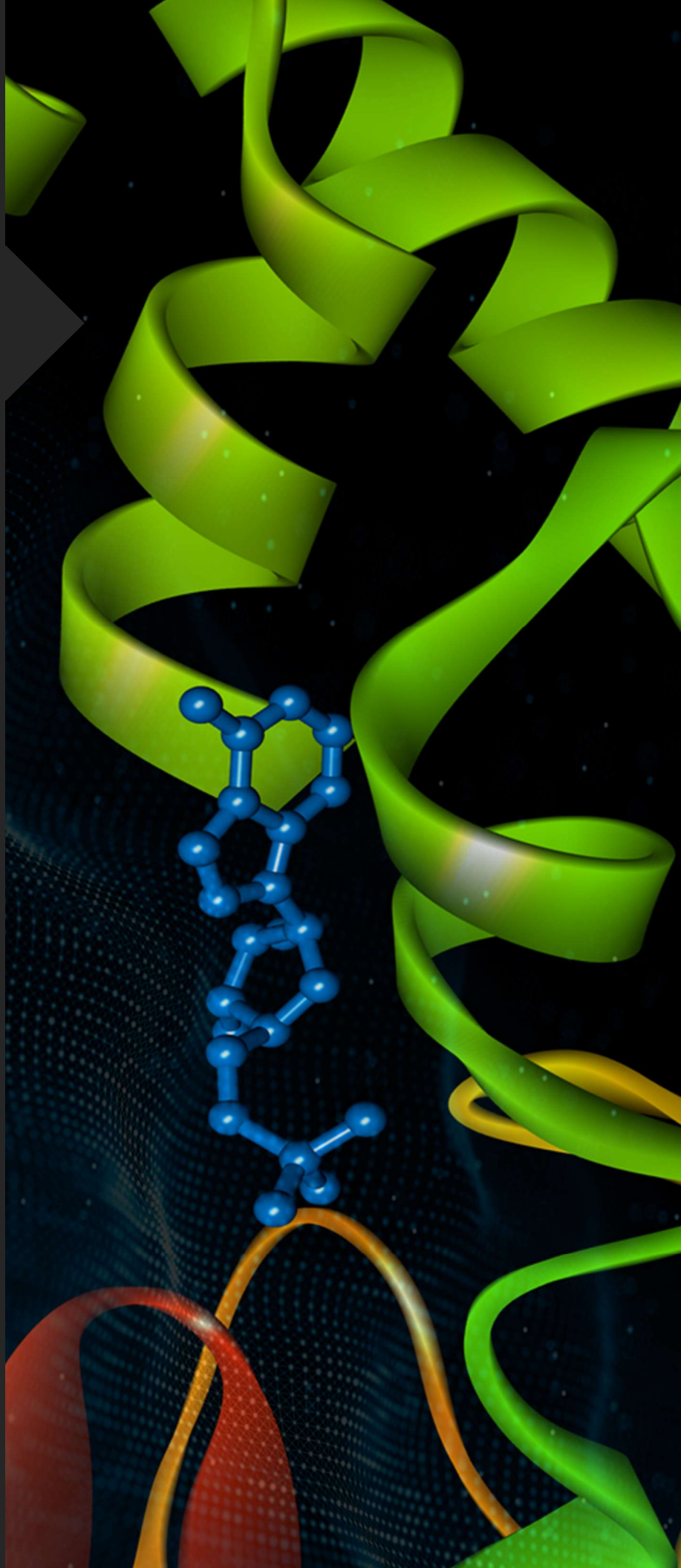
PATTERN COMPUTER®

AI-Assisted Drug Discovery

Fostering Transformative Research through Pattern Discovery



Pattern Computer Inc.

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Fostering Transformative Research through Pattern Discovery

AI-Assisted Drug Discovery

Who we are and what we do

Pattern Computer Inc. (PCI) is an AI-powered technology company that uses its pattern discovery platform to deliver breakthrough discoveries across a number of domains such as biomedical science, material science, aerospace, and veterinary health. For example, in personalized medicine we are discovering therapeutically exploitable relationships within complex, high-dimensional biomedical data to find therapeutics for difficult-to-treat diseases.

Using our innovative pattern discovery platform we have identified **two sets of potential combination therapy candidates for Triple-Negative Breast Cancer** (TNBC), one of the most aggressive subtypes of breast cancer (see our press release). What makes this discovery significant? TNBC accounts for 15-20% of all breast cancers and tends to have a more aggressive phenotype and a poorer prognosis due to the high propensity for metastatic progression. Due to lack of known therapeutic targets in TNBC, hormonal therapies and HER2-targeted agents are ineffective with this group of tumors. Current treatment options for most patients are limited to cytotoxic chemotherapy. Despite initial responses, multidrug resistance develops frequently and rapidly, and if chemotherapy fails, in the absence of subsequent treatment options, most of the patients succumb to their disease within 3 to 5 years. Therefore, we set out to discover polythetic patterns of interacting genes in a leading breast cancer related genomics dataset and translate these patterns into potential molecularly-targeted combination therapies for TNBC, seeking to address a critical unmet need. This paper describes our progress toward our goal of developing much-needed therapeutic pathways for the treatment of TNBC patients.

Higher-order Interactions

Diseases such as Alzheimer's, breast cancer, and diabetes are regulated by multiple interacting genes, some providing a protective effect and others contributing to the disease pathogenesis. These interactions are critical for gene regulation, signal transduction, biochemical networks, and numerous other physiological and developmental pathways. The traditional approach based on 'one-gene, one-target, one-mechanism' to understand the genetic basis behind these diseases is not effective. With the advent of high-throughput tools, we can gather hundreds of thousands of data points from cells, with the transcription level used as the measured phenotype. As a result, it is now possible to identify gene relationships, networks, and epistatic interactions at a systems level. However, the search-space for possible signatures of interactions is intractably large, so computational methods that limit the experimental effort of validating the interactions for therapy are highly desirable. Methods exist for identifying two-way relationships or 'hypothesis-driven' higher-order interactions. In addition, many "black box" machine learning architectures take

advantage of complex interactions. However, extracting them for human exploration and hypothesis generation remains a foundational challenge for the field. "Open box" procedures, like forward regression, become computationally prohibitive for even relatively small datasets.

How PCI's tech is solving hard biomedical problems

This is where PCI's machine learning technology excels. Our proprietary algorithms allow us to search for higher-order interactions in large genomic datasets, within supervised as well as unsupervised learning frameworks, revealing many important aspects of genomic architecture. We discover pathways, or relationships between pathways, rather than individual genes - enabling fundamentally new types of genetic and genomic studies. In fact, we have **demonstrated the capacity of our algorithms to learn 6th order interactions in a search space larger than 10^{22} at the same computational cost as the identification of individual genes**. This represents a substantial advantage over existing approaches and uniquely positions our technologies for the discovery of complex, nonlinear interactions permitting inquiry into the higher-order mechanisms underlying functional regulation. Viewing complex diseases through the lens of genomic landscapes, rather than individual genes, is helping us better understand the pathobiology of diseases and develop new, effective, and personalized treatment options for combating them.

How it works

First, we extract the most relevant features out of high-dimensional data. We can do this across many types of data; examples include gene expression, mutation, and methylation data. The selection criteria varies based on the data considered (e.g., frequency in mutational data, variability in gene expression data). This filtered data is fed into our proprietary **Pattern Discovery Engine™** that finds underlying associations between features and is key to understanding the molecular mechanisms of diseases. The resulting associations between genes can be visualized by constructing 3D network graphs. These gene associations are then parsed through post-processing filters to identify clinically-actionable gene associations. Upon identification of relevant gene interactions, we work backward to figure out how the drugs targeting these genes affect a given disease, assessing their therapeutic benefit in order to generate testable experimentations (Figure 1). We then assess the results set that supports the link between repurposed and/or combination therapies and the disease type. The most promising candidates are then submitted for biological evaluation.

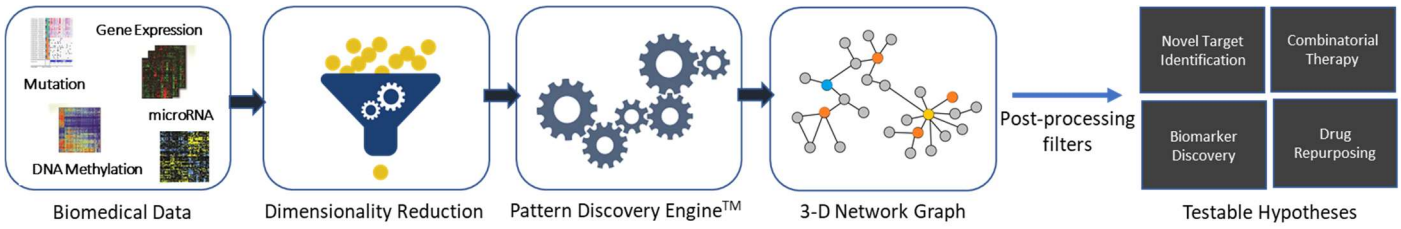

Figure 1. An illustration of PCI's approach to identifying biologically relevant patterns.

What makes our approach unique?

- Our approach is data-driven and is less dependent on theoretical presuppositions making it **hypotheses-free**. We analyze high-dimensional data with no preconceived notions. This shift elevates the data to a primary function of revealing complex structures to yield novel and often surprising correlations. It provides an important advantage over the conventional pharma drug discovery model as it allows researchers to examine a vast number of pathways simultaneously identifying a smaller subset worthy of targeted investment and clinical study.
- PCI's AI platform can predict, within weeks, gene association networks relevant to a disease, allowing identification of actionable higher-order gene interactions. This enables us to pursue a commercial pathway **from discovery to clinical trials within 12-24 months** when focusing on repurposed or combination therapies, making the drug discovery process faster, cheaper, and with lower failure rates; certainly so when compared to traditional drug discovery of novel target pathways stretching 10-12 years at an average cost of US$2.6 billion from discovery to launch and with 90 percent of drugs washing out in clinical trials (Figure 2).
- Our pattern discovery platform can be easily integrated into a comprehensive and flexible framework for data mining and actionable knowledge discovery allowing it to **operate equally successfully in any domain, including financial services, energy, transportation, among others.**

We have validated our technology by identifying relevant patterns in genomics data sets and comparing against experimentally established gene associations published in the literature.*

What we Discovered in Breast Cancer

We applied our tool to the integrated genomic/ transcriptomic data set released by Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) to identify the associations between complex gene expression patterns that can then be used to identify novel target(s), repurposed drugs and novel combinatorial therapies. This data set contains gene-expression values for 24,367 genes from 1,904 breast tumors. The goal was to map the gene expression architecture that underlies breast cancer into human-navigable representations and to systematically extract "previously unknown" structures residing in them. This data has been published for some time and researchers have had over a decade to extract value from it. Consequently, it is safe to say—the discovery of new and interesting insights from such a well-examined data set would be a highly-noteworthy achievement.

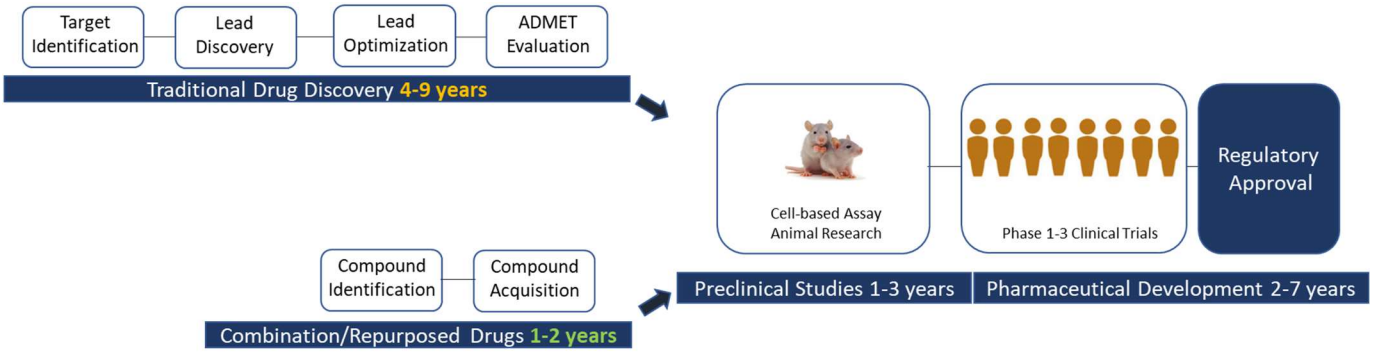

Figure 2. PCI's AI-Assisted Drug Discovery - making the process faster, cheaper & with lower failure rates.

Breakthrough potential in Breast Cancer research

Application of our proprietary algorithms to this data set revealed several known as well as novel patterns. These patterns or gene associations were subjected to post-processing to identify genes and gene interactions that were actionable, i.e. genes for which approved or clinical-stage compounds were available. While known associations served to validate our algorithms' capability, novel patterns were used to formulate testable experimentation pathways – in the form of molecularly-targeted repurposed and combination drugs. These combinations were submitted for biological evaluation in breast tumor organoid models at the world-renowned Lawrence Berkeley National Laboratories. Among the limited number of potential candidates submitted, two drug combinations demonstrated significant synergy in killing cancer cells, with low to no cytotoxic effects on normal cells in *in vitro* breast tumor organoid assays. Follow-on animal studies at a leading global clinical research organization further supported the promise and validity of our combinations as treatment options for TNBC. One of the inhibitor combinations displayed good synergistic antiproliferative response in two human TNBC cell lines-derived xenograft models. This combination was well-tolerated even at high doses.

Our work ahead

As next steps, we have advanced our potential combination therapy candidate for further pre-clinical validation through targeted *in vivo* studies with a global clinical research laboratory. Our goal is to demonstrate that the combinatorial drugs represent therapeutic enhancements in drug efficacy while countering toxicity, side effects and drug resistance often seen with standard-of-care chemotherapies - or with monotherapies - acting against this menacing breast cancer subtype.

We are most encouraged by these results and the path ahead. And given our capability for discovering high-order interactions in genetic data, we are actively and aggressively directing our platform tools toward drug discovery efforts in the search for equally promising treatment candidates for other complex and intractable disease types, all in furtherance of our mission to *solve the most pressing health and societal problems as the global leader in pattern discovery.*

To learn more about Pattern Computer Inc. and how to partner with us, e-mail us at *inquiry@patterncomputer.com*, or visit our website at www.patterncomputer.com.