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Tackling onerousness drug development process through cost-effective genomic analysis platforms

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A successful drug is priced to cover the cost of the R&D which can be avoided by identifying drug target modalities through a whole-genome analysis approach, explains Bertrand Adanve, Founder & CEO, Genetic Intelligence (USA)

The limitations of the existing drug discovery paradigm reveals that there are still no effective prevention or real cures for most complex inherited diseases such as amyotrophic lateral sclerosis, Alzheimer's disease, idiopathic pulmonary fibrosis and cancers. Despite accelerating genome sequencing and creating CRISPR genetic therapy modalities, improving speed and cost of drug discovery by adopting targeted drug discovery methods has become a crucial therapeutic need of the hour. Genetic Intelligence (GI), a deep-tech, drug discovery company is at the forefront of developing solutions to creating effective medicines for diseases with unmet needs, by leveraging on AI and neural network. ***Bertrand Adanve, Founder & CEO at Genetic Intelligence (USA)*** provides further insights on these precision gene therapeutics. Edited excerpts;

How do you describe Genetic Intelligence (GI) Platform design for a swift drug target discovery by eluding undruggability limitations?

The Genetic Intelligence (GI) platform is founded upon our two core beliefs to (a) explore the unexplored 99 per cent of the genome to identify genetically defined targets and (b) drug the target at the RNA transcript stage using small molecule or oligonucleotide modalities. The GI platform was pioneered to address the key challenges facing drug discovery today.

The root causes of the lack of effective drugs against many complex inherited diseases are two-fold:

1. The field's collective inability to produce valid, predictive models for such diseases, leading to the lack of well-validated genetic targets. Over 99 per cent of the genes and/or genetic features that cause multigenic diseases remain unknown. Lack of effective tools to analyse the whole genome to uncover the roles of these non-coding genes in disease are creating "undruggable" perspective to an ailment.
2. The reliance on drug modalities that have limited ability to achieve modulation of their genetic targets in a safe and effective way with minimal off-target effects.

Genetic Intelligence has solved these two challenges by pioneering a whole genome analysis platform that blends genetic principles with proprietary artificial intelligence (AI) algorithms to identify actionable disease targets (whether coding or non-coding) that can be leveraged for effective cures. This is followed by the design of oligonucleotide- or small molecule-based modalities to modulate the targets at the RNA-transcript level, which circumvents the limitations inherent to protein targeting and allows effective and safe targeting of any genetic target (whether coding or non-coding).

The full Genetic Intelligence pipeline is employed end-to-end in diseases where a causal target or otherwise effective target isn't yet known. But in diseases where there are validated targets that are undruggable at the protein level, the second part of our platform is directly engaged, i.e., RNA-targeted drug discovery. Thus, our target discovery and drug discovery capabilities can be fully independent of each other.

How is GI Platform solving the challenges at the onerousness drug development process while reducing drug development cost?

It is a well-known statistic that more than 9 in 10 drugs that enter clinical trials fail, not to mention the vast number of candidates that fail at earlier stages of the drug development process prior to entering clinical trials. This onerous statistic is due primarily to the lack of demonstrable efficacy of drugs.

This challenge is probably the key reason resulting in the high cost of drugs that reach the clinic, since the drug needs to be priced to cover the cost of research and development leading to the successful drug, as well as cover the cost of all the failed drug candidates along the way.

The GI platform addresses the heart of this issue by overcoming the two key reasons for the lack of efficacy of drug candidates: going after the wrong target and/or using drug modalities that are ineffective at modulating the target. The first two layers of the GI platform, Bergspitze and Franklin, address the problem of identifying novel, actionable targets for a disease.

GI's technology overcomes limitations at traditional approaches for whole genome analysis and identifies drug modalities to modulate a target. The GI platform relies on validated computational models to rapidly generate ASO and rSM designs that eliminate the need for expensive and time-consuming experimental approaches.

All these factors lead to efficacious drugs with reduced side effects, faster time to market, lower development costs, and can benefit from regulatory acceleration programmes such as the FDA's fast track, orphan drug and breakthrough designations. Patients and society-at-large can benefit from an accelerated target-to-therapy pipeline, decreased risk of failure in clinical trials, and more effective and affordable treatments since research and development is less costly.

Can you elaborate GI's therapeutic approach in developing small molecule or oligonucleotide modalities for precision therapeutics?

To produce precision therapeutics, the GI platform relies on four primary layers: Bergspitze, Franklin, Orisha, and Lea.

- Bergspitze is a biology-aware artificial intelligence (AI) stack that takes in whole genome sequences (WGS) from disease patients and tames the noise of the whole genome to pinpoint the disease causing genetic positions.

- Franklin is the interpretation infrastructure that takes in the output from Bergspitze and provides a coherent etiology model for the disease by confirming targets to leverage for a cure.

- Together, the Bergspitze and Franklin layers address the first challenge of identifying novel, actionable disease targets from across the whole genome.
- The Orisha layer designs RNA-targeted molecules to modulate a target's RNA transcript at the sequence level via antisense oligonucleotides (ASOs) or at the structure level via RNA-targeted small molecules (rSM). In this layer, intensive checks of the ASO or rSM designs are performed computationally against the full transcriptome to minimise potential off-targets, thus ensuring that the ASO or rSM candidates are highly specific to the given target.
- The final layer, Lea, confirms experimentally the novel disease targets and advanced therapeutic candidates produced by the computational layers using patient-derived iPSC (stem cell) assays, which are human and disease-relevant models.

Could you share the therapeutic pipeline at GiTx (Genetic Intelligence therapies) predictive models curing chronic conditions and APAC market access strategy?

GI's therapeutic pipeline is currently focused on diseases with high unmet need, i.e., significant global patient population pool coupled with lack of effective curative drugs. These include neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD) and Alzheimer's disease, as well as idiopathic pulmonary fibrosis and certain cancers. However, GI platform is disease-agnostic and can be applied widely to diseases where there are no known effective targets and/or to cases where there are validated genetic targets but those are difficult to modulate with existing drug modalities.

The power and potential of GI's technology platform is best illustrated using the example of our Amyotrophic Lateral Sclerosis (ALS) programme, which was built entirely from scratch using GI's platform. Whole genome sequences of ALS patients were analysed using Bergspitze and Franklin to identify six novel genetic targets that were previously unexplored in ALS. We have validated one of the target genes which upon modulation improves survival and lowers a key disease-causing biomarker. This achievement validates the power of GI's platform to discover novel, actionable and effective genetically defined targets. Subsequently, we used Orisha to design ASO drug candidates against GI's validated ALS target. GI's cancer programme employs our RNA-targeted small molecule discovery capability.

GI validates novel genetic targets and drug candidates for diseases with an AI-driven, drug development hub in the Asia Pacific with regional presence in Singapore. GI is open to collaboration opportunities on our existing internal programs to address diseases of their interest whether starting at the target discovery stage or starting at the RNA-targeted drug discovery stage.

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