Jake Rubens: Somatic Genomics

Insights for drug discovery from trillions of genomes

One of the main drivers of modern drug discovery is genomic science, which holds the keys to understanding biology, evolution and disease. Insights derived from genomics can be translated into novel medicines and transform healthcare. In fact, a recent analysis found that new drug mechanisms supported by genetic evidence are around 2.6 times more likely to succeed than those without[1]. To continue unearthing breakthrough medicines, we must continue to mine the vast amount of information encoded in our DNA.

Traditional DNA sequencing technologies read the 'representative' genome of a collection of cells, failing to capture the genetic differences between each individual cell. Recent advancements in DNA sequencing are revolutionising our comprehension of genetic variability, revealing that each cell has a unique genome sequence, and redefining our understanding of cellular variability.

The genetic changes that occur in the genome of individual cells are called somatic mutations, and they occur at profound rates in every organ system [see table]. The field of somatic genomics, which emerged in the last five years, analyses somatic mutations to provide a comprehensive view of the genes, proteins and pathways that contribute to disease, and it has deep implications for drug discovery research[2]. Within each tissue, evolution and natural selection act at the cellular level to conduct a process akin to cellular clinical trials, testing somatic mutations that may protect from, drive, or predispose cells to disease. By identifying these somatic mutations, we can facilitate the development of novel medicines that imitate or inhibit a mutation's impact.

When we founded Quotient Therapeutics in 2022, we set out to build a comprehensive platform to leverage insights from studying somatic mutations to create new medicines. Our efforts were made possible by several innovations that have driven advancements in this field and are integrated into our somatic genomics platform. These include laser-capture microdissection, which enables the isolation of diseased or healthy cells from an individual's tissue to facilitate somatic genomic analysis,[3] and nanorate sequencing or Nanoseq, a single-molecule DNA sequencing technology that has up to a 10-million-fold lower error rate than next-generation sequencing technology. By significantly improving sensitivity, Nanoseq facilitates comprehensive somatic genomic analyses[4].

Our platform produces a vast amount of data and benefits from proprietary computational methods where artificial intelligence and machine learning play a central role. We identify patterns and correlations by integrating our somatic genomics data with complementary genomics datasets, such as germline genetics and transcriptomics. By integrating these wet lab and dry lab technologies in our somatic genomics platform, we are expanding the frontier of genetics.

We expect that drugs which modulate the targets identified via somatic genomics will have a higher probability of success than those lacking genetic support, akin to targets identified via germline genetics[1]. The emerging somatic genomics field has already discovered potentially high-impact drug targets in many diseases, including metabolic dysfunction-associated steatohepatitis (MASH) – formerly known as nonalcoholic steatohepatitis (NASH)[5]. MASH is

Table: Average number of somatic mutations per cell in human tissues

Tissue Type	Average number of coding mutations per cell*
Colon	2,180
Liver	1,650
Skin	1,450
T-cells	1,020
Brain	800
Lung	640
Pancreas	620
Kidney	210

*Observed from representative middle-aged healthy patients[2] (and additional data on file, Quotient Therapeutics)

Flagship Pioneering and Quotient

Flagship Pioneering Inc is a bioplatform innovation company based in Cambridge, US, that invents and builds platform companies, each with the potential for multiple products that transform human health and sustainability. Flagship founded Quotient Therapeutics in 2022. It also has an in-house drug development unit called Pioneering Medicines that is dedicated to conceiving and developing a broad portfolio of life-changing treatments for patients built from Flagship's innovative platforms. Pioneering Medicines explores and identifies new product concepts which are then advanced jointly with Flagship's bioplatform companies. Pioneering Medicines also partners with external collaborators to apply its unique approach to partners' R&D priorities. These strategic alliances accelerate therapeutic innovation by bringing together partners spanning the full spectrum of drug discovery, development and production. Its collaborators include Novo Nordisk A/S, GlaxoSmithKline, the Cystic Fibrosis Foundation and Pfizer Inc. On 28 August 2024, Flagship announced a new agreement with Pfizer Inc under which Pfizer will work with Quotient to analyse somatic mutations that occur in diseased patient tissue to inform drug discovery and development.

the leading cause of liver disease worldwide. Recent work demonstrated that hepatocytes with protective somatic mutations have a growth advantage in the liver of MASH patients,[5] and that inhibiting these same genes in the liver of wild-type mice is efficacious in treating MASH[6]. Beyond MASH and cardiometabolic disease, Quotient's somatic genomics platform has the potential to inform transformative treatments in many therapeutic areas, including immune and inflammatory diseases, immuno-oncology, renal diseases, cardiovascular diseases, respiratory diseases, infectious diseases, neurodegenerative diseases, rare diseases and ageing.

By offering unprecedented insights into the genetic variability inside our bodies, somatic genomics is redefining our understanding of biology and paving the way for novel therapeutics. As we continue to develop and deploy this technology, Quotient's platform promises to propel medical innovation forward.

Quotient Therapeutics is a Flagship Pioneering company that was founded in collaboration with leading scientists at the Wellcome Sanger Institute and the University of Texas Southwestern. Recently, we announced a partnership with Pfizer, where we are applying our somatic genomics platform to identify new drug targets for renal and cardiovascular diseases. This partnership marks the first of what we anticipate to be many, as we recognise the need for collective expertise and collaboration to fully realise the vast therapeutic potential of somatic genomics. I cannot wait to see the potential cures we will discover.

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