Genome Architecture Theory shakes up cancer research

It's an inconvenient truth that after 50 years of concerted research and untold billions of dollars in funding every year, a cure for cancer remains elusive. Perhaps the problem sits with the conventional view of cancer. Henry H. Heng, a professor of molecular medicine at the Wayne State School of Medicine in Detroit, Michigan, suggests we need to see the bigger picture and even rethink our understanding of evolution. His Genome Architecture Theory is telling and provocative, which is why it's attracting interest from an unlikely collaborator who sees progress in disruption.

It's probably true that every person who has lost a loved one to cancer has wondered at some point why there isn't a cure. It's a fair point, given the tens of thousands of scientists who have spent endless hours and billions of dollars in cancer research every year for over 50 years. The reason generally given for cancer's resolve is that there is no single 'cancer' and that every cancer in every patient is, to a degree, different. There is some truth to that, although there could be a simpler but more sensational reason: our fundamental understanding of cancer is wrong. If that is true, it could explain why common treatments for cancer seem to miss the mark.

One cancer researcher supports such reasoning. Dr Henry H. Heng is a professor of molecular medicine, genetics, and pathology at the Karmanos Cancer Institute at the Wayne State School of Medicine in Detroit, Michigan, in the US. His main research area is molecular cytogenetics and cytogenomics – the relationship between chromosomes, gene expressions and cell function/behaviour – in somatic cancer cells. Over decades of research, Heng has noticed that when cells become 'cancerous' or tumour cells undergo significant phase transitions – say from being localised to metastasising or from drug sensitive to drug resistant – most of them display dramatic changes in their karyotypes – the number of chromosomes and the genes' ordering of the cell's chromosomes – to the point that they are fundamentally different cellular organisms. Moreover, he illustrates how these significant changes occur when the cells are exposed to high stress during a crisis – such as an environmental event or medical treatment – resulting in a chaotic 'rewiring' of the entire genome. According to his new theory, the genome is not simply a 'bag of genes' but represents higher-order system information that organises gene interactions. Thus, chromosomal changes are actually the key drivers for cancer evolution.

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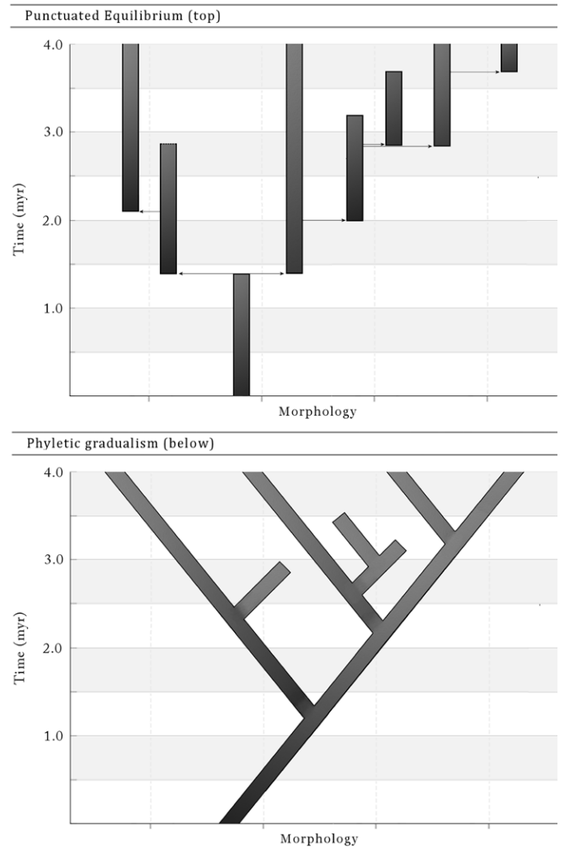
This theory clashes significantly with the standard understanding that cancer develops when a few common, specific gene mutations accumulate in the body, triggering the production of aberrant cells. Importantly, whether benign or malignant, these cells are considered the host's cells, just dysfunctional, displaying out-of-control growth. Therefore, treatment should involve targeting these bad gene mutations or maximally killing as many cancer cells as possible, battering the aberrant cells into submission. Heng disagrees, saying cancerous cells are so different in their genome architectures they're akin to a different cellular species in the host. Subsequently, Heng believes 'standard' gene mutation-based cancer theory demands a complete rethink, as do some treatments it supports, such as chemotherapy that can induce drug resistance and make cancer more deadly. Suffice to say, this rankles the pantheon of cancer researchers who reject non-conformism and the idea they could be wrong. But here's the rub: Heng has history, science, and precedent on his side.

THE MAVERICKS

Science doesn't know everything; if it did, it would stop. The gaps in our scientific knowledge close at a seemingly glacial pace, primarily due to the immeasurable scope of the study – the natural world in all its vastness and complexity – and the speed at which research takes place. Traditionally, the picture we develop of our natural world comes through the meticulous, step-by-step joining of microscopic pieces of insight derived from growing data – like parts of a puzzle – around an established framework of thinking: a theory. But every now and then, a maverick – or non-conformist – scientist with a critical eye comes along and suggests the framework is wrong, and we need to rethink our approach.

Such scientists are essential to the very health of science – they encourage us to re-examine conventional wisdom, especially when that wisdom seems significantly flawed. The fundamental surgical process of hand scrubbing was once considered non-conformist. Einstein unwound Newton's clockwork universe where time and space were absolutes. Lynn Margulis shocked biologists in the late 1960s with her theory that vital structures within eukaryotic cells, upon which all complex life is based, came from simple bacteria swapping genetic code – an idea now considered mainstream. And for decades, the notion that bacteria caused stomach ulcers was met with scorn in scientific circles until two Australian researchers proved dramatically otherwise, earning them the Nobel Prize in Physiology or Medicine in 2005.

Heng fits the bill of a science maverick: a senior, highly accomplished, and meticulous researcher who has, through insight, contentment in chaos, or a dissenting disposition, investigated a problem from a different angle. Yet his idea is hardly surprising: it's evidenced in evolution.



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The punctuated equilibrium model (top) consists of morphological stability followed by rare bursts of evolutionary change. In contrast, phyletic gradualism (bottom) is a more gradual model of evolution linked by various intermediate populations. When originally proposed by Eldredge and Gould, punctuated equilibrium was controversial. Genome Architecture Theory reconciles the two models and shows how both are necessary to fully explain the fossil record as well as cancer evolution.

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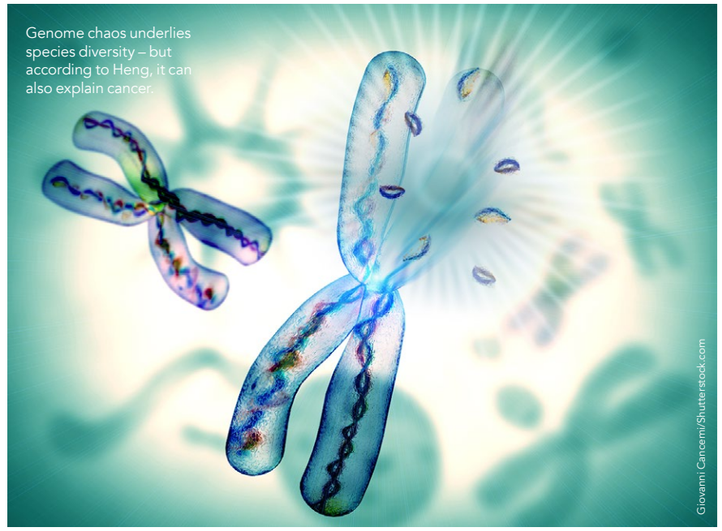
THE ALIEN IN OUR BODY

Darwin's theory of evolution was based on gradual, minuscule genetic changes over long periods of time. This 'micro-evolution' was determined by the successful genetic traits of successive generations of individuals within a species adapting to their surroundings. However, this doesn't explain fossil records that show long periods of micro-evolution, or seeming stasis, punctuated with occasional 'macro' leaps in evolution. This 'punctuated equilibrium' could only occur if there were two phases: a macro-evolution spurred by some external event that triggers a dramatic and seemingly chaotic, yet successful, rewiring of a species' genome architecture, followed by micro-evolution – the more Darwinian genetic 'fine-tuning'.

For Heng, just as this genome chaos creates species diversity, so too does it explain the disordered cellular

variegation we call cancer. Speciation and cancer metastasis are both forms of chaos-triggered macro-evolution; ergo, a clump of cancerous cells in a person's body is like a new species, as are the evolutionary 'leaps' of cancer's emergence. Such an approach to cancer may sound far-fetched, but, as such, it does have evidence in the fossil record. That doesn't mean science is willing, just yet, to accept Genome Architecture Theory.

However, some believe it's time for cancer research to have its own evolutionary leap. For that, it needs an injection of energy, a spark to initiate a chaotic burst – a radical rewiring of cancer research's architecture. Given Heng's maverick status, it's doubtful it'll come from academia. Luckily, he's been dealt a rather fortunate hand.


Genome chaos underlies species diversity – but according to Heng, it can also explain cancer.

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It is time for Heng and other aligned mavericks to go all-in and disrupt the evolutionary establishment, colloquially known as Modern Synthesis and neo-Darwinism.

THE POWER OF DISRUPTION

Rafe Furst is a former World Series of Poker champion with a master's degree in computer science and artificial intelligence from Stanford, who turned his deft skills towards tech entrepreneurship and investing in big ideas and maverick individuals. He has also raised considerable money for cancer research and was elected to the board of the Prevent Cancer Foundation. His and Heng's paths crossed at a conference where Heng presented his theory of genome chaos. Furst was fascinated with the idea and became frustrated that it wasn't gaining traction with other researchers. His high-stakes competitive streak kicked in, and he decided to challenge academic inertia.

In a recent submission to the journal *Progress in Biophysics and Molecular Biology*, titled 'The Importance of Henry H. Heng's Genome Architecture Theory', Furst presents Heng's key arguments in simple language ('Inheritance is not precise, it's fuzzy') and sound logic, stripped of confusing academic trivialities. He employs unpretentious analogies and provocative wording, breaking down the intricacies of Heng's theory into 11 basic points. For example, he explains that the whole genome (not the gene) is the primary unit of heritable information upon which two-phased evolution (genome alteration-mediated macroevolution and gene mutation-mediated microevolution) works.

In effect, Furst pushes Heng's Genome Architecture Theory into the open, celebrating its maverick nature and scientific rigour. His message has all the confidence of a master poker player: it is time for Heng and other aligned mavericks to go all-in – collectively – and disrupt the evolutionary establishment, colloquially known as Modern Synthesis and neo-Darwinism.

RATTLING CAGES

Science is watching what will happen now, probably intrigued at Heng and Furst's alliance. At first glance, the two make an unlikely pair: the quiet, bookish, seasoned academic scientist and the self-assured entrepreneur and impact investor. But they are bonded by an unwillingness to bow to convention in the quest to revolutionise cancer research. They're also not holding back. Genome Architecture Theory is bigger than cancer research – it's part of a more significant shake-up of evolutionary theory. And Heng and Furst are not alone in their efforts, as the movement has been pushed forward recently by some big names in biology, including James Shapiro and Denis Noble (www.thethirdwayofevolution.com/people), as well as another entrepreneur-turned-evolution-maverick, Perry Marshall (evo2.org). Cages are being rattled, and scientific egos look likely to fall.

Heng has spent decades testing, retesting, and fine-tuning his Genome Architecture Theory, more importantly, arguing for its place in rethinking our understanding of cancer. Two things to this point are true: while scientific knowledge is sometimes upended for the good by non-conformist thinking, the inertia of scientific conformity is largely uninviting to those who challenge the status quo; and, after 50 years of conformist thinking around cancer research, treatment has changed very little and a cure still seems far away. Heng has found a valuable ally in Furst and the other mavericks. This combination of scientific gravitas and entrepreneurial disruption may now be pushing the field closer to understanding the true nature of cancer, which is a prerequisite for more successful treatments and ultimately (if possible) a cure.

Behind the Research

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Research Objectives

Dr Henry Heng's Genome Architecture Theory is a new paradigm questioning the status quo of genomic and evolutionary theories.

Detail

Bio

Dr Henry Heng is a professor at the Center for Molecular Medicine and Genetics at Wayne State University School of Medicine. He received his PhD from the University of Toronto's Medical Genetics Department. His current research focuses on developing the Genome Theory of Cancer and Organismal Evolution, which emphasises karyotype-coded system information and separates macro- and micro-evolution by different genomic mechanisms.

Rafe Furst is an entrepreneur, investor, and catalyst for big ideas. Furst holds a degree in symbolic systems and a master's in computer science and artificial intelligence from Stanford University.

Collaborators
Perry Marshall

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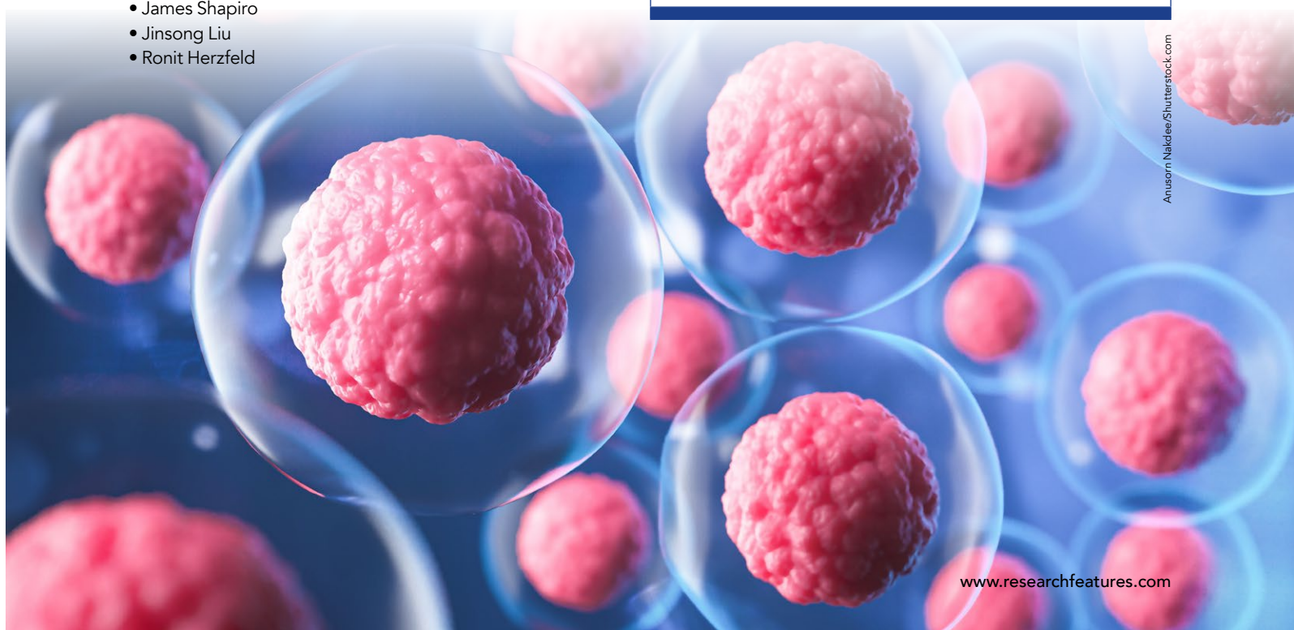
Personal Response

What would it take for Genome Architecture Theory to develop sufficient traction within cancer research?

"Future research should focus on genome instability rather than specific gene mutations when there are so many; treatment should avoid inducing genome chaos by current harsh treatments. At the conceptual level, we need to realise the limitations of the current evolutionary framework. Rather than using gene mutation-focused reductionist approaches, we should fight cancer according to the genome and information-based evolutionary concepts."



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