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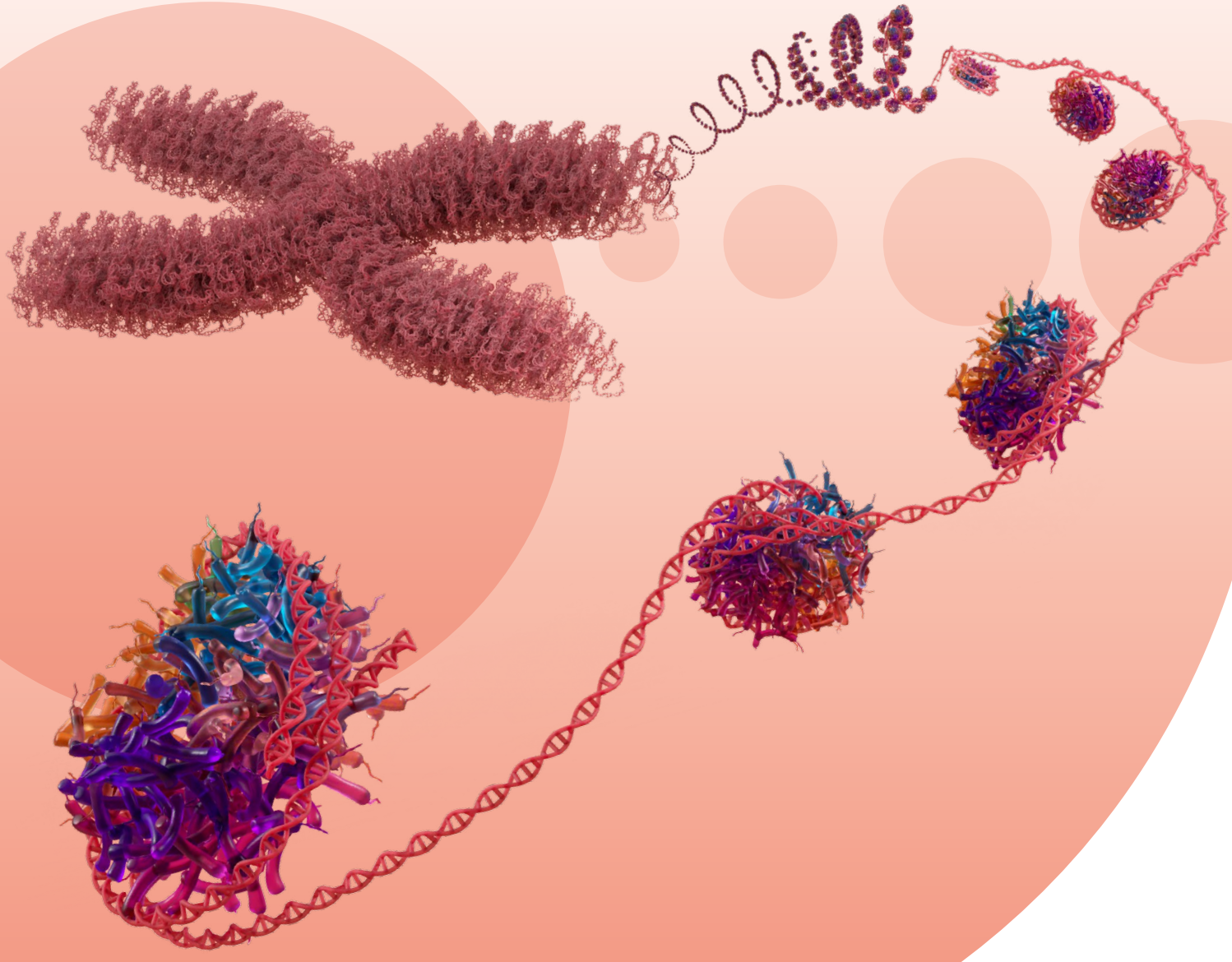
The epigenetic keys to unlocking the full potential of immunotherapy.



Volition

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Introduction

Epigenetics is the key to unlocking the full potential of cancer therapy, including immunotherapies, by revealing deep insights into how the body reacts and responds to medication.

The rise of novel immunotherapies has created bulging pipelines with thousands of products progressing through R&D and into clinical trials, strengthening their position as a potent weapon to combat cancers that resist conventional treatment.

The Cancer Research Institute recorded that the number of immune-oncology drugs either approved or in development had risen by 233% from 2017 to 2020 with the climb likely to continue as nations emerge from the pandemic burdened with backlogs in cancer treatment.[1]

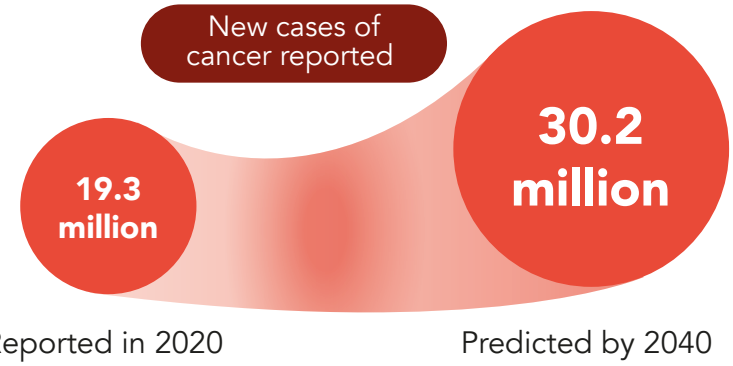
But, despite their promise, only 20% to 40% of patients respond positively[2] because tumours can evolve, downregulating immune recognition and activation which, in turn, increases immune checkpoint activation and can create an immuno-suppressive tumour microenvironment.

In effect, the immunotherapy is neutralized, or its efficacy vastly reduced so that tumours can progress while patients suffer a range of side effects from an ineffective treatment. Having markers that are able to predict their treatment response or ineffectiveness would improve patient outcomes and save millions of dollars.

This is more than a scientific and medical inflexion point.

Cancer incidence and mortality are rising sharply

Statistics from the World Health Organisation's International Agency for Research on Cancer.[3]



The epigenetic keys to unlocking the full potential of immunotherapy.

Understanding how patients will respond to immunotherapy when treating a specific cancer is critical to targeting therapies to the right patient at the right time while also accelerating diagnostics by revealing biomarkers that enable clinicians to tackle tumours earlier and with more precision to reduce mortality.

Immunotherapy drugs are potentially transformative, but they can activate a broad range of immune cells and trigger severe auto-immune reactions. Predicting who will be a non-responder will sharpen clinical research focus, save treatment costs, and spare patients from unnecessary side-effects.

Improved identification of biomarkers needs to be twinned with immunotherapy's potential which is where epigenetics plays a crucial role. Research has demonstrated that epigenetic alterations are present at the early stage of disease and that these alterations increase cancer cell proliferation and allow cancer cells to evade chemotherapy and host immune surveillance.

Epigenetics is a core component of biology and alterations can be found across all forms of cancer providing a route for identifying biomarkers associated with cellular mysregulation, disease progression and the ability to resist and evade therapy.

The composition and location of nucleosomes – the repeating, structural units of chromosomes – can be altered by treatments and disease progression and immune response is triggered.

"Epigenetics is at the heart of our science, and it is what provides us with the signals to understand how a tumor reacts to a drug."

"From it, we can predict the disease pathway and the immune response to generate critical understanding for clinical researchers and drug developers," says Terry Kelly, Chief Innovation Officer at VolitionRx, which is dedicated to revolutionising the diagnosis and monitoring of life-altering diseases through epigenetics.

"With this knowledge, we can ask what is happening in the cell type and how it functions when a type of drug is introduced. It means you can ask the hard questions about your drug and the value of these biomarkers can apply across all biology."

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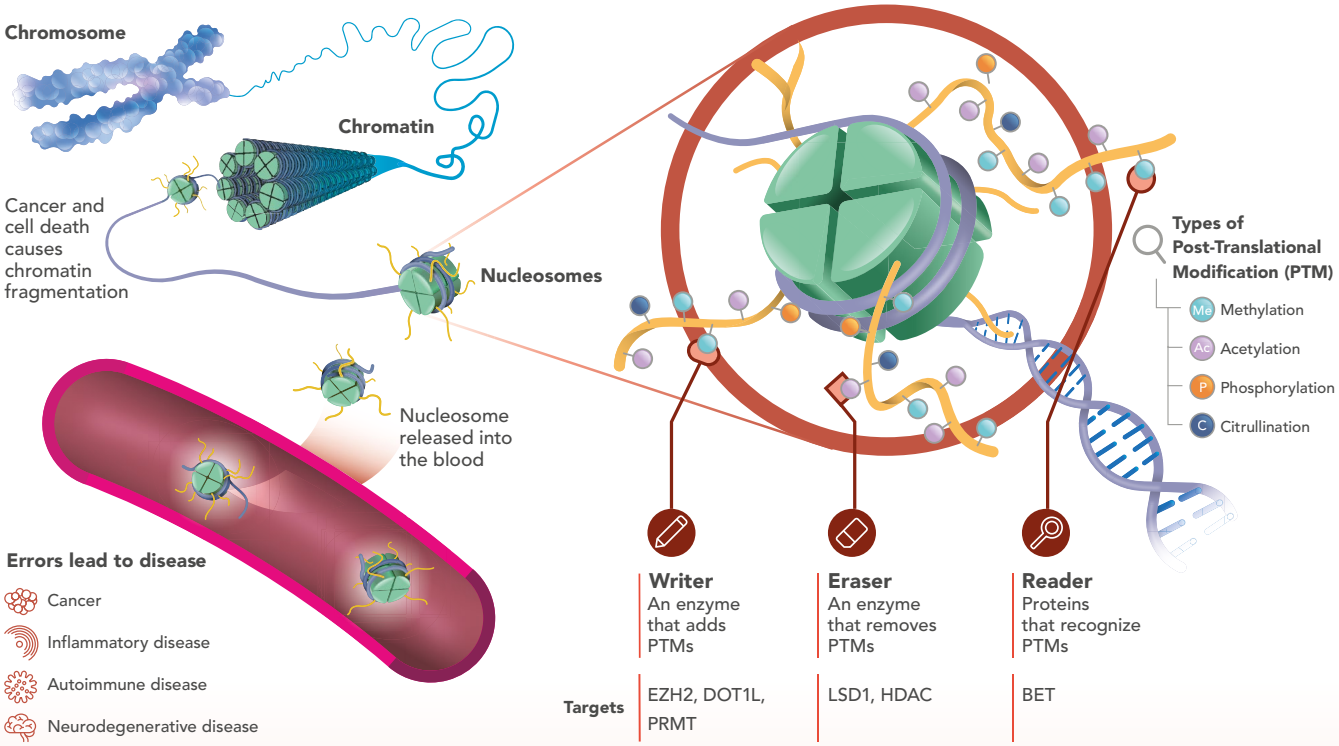
The Role of Nucleosomes

Cancer cell death results in chromatin fragmentation and the release of nucleosomes into the blood. This activity can be measured and monitored as a clear indicator of disease progression and response to treatment, making nucleosomes a rich source of biomarkers across all cancers.

With epigenetic alterations present throughout tumour initiation process through to metastasis, further studies have demonstrated that modifications on histone proteins from the nucleosome can indicate the presence of cancer, thus enabling early detection and targeted treatment.



Deciphering how to measure nucleosomes and their modifications both swiftly and sensitively has been the driving ethos of Volition, the multinational epigenetics company whose proprietary Nu.Q® nucleosome quantification platform and its range of state-of-the-art assays is generating epigenetic intelligence for developers and scientists across disease model development, pre-clinical testing and clinical studies.

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Nucleosomes contain more than 200 possible modifications that are fundamental to every cellular process and measuring and monitoring nucleosome levels and modifications in circulating blood has the potential to aid diagnosis, prognosis and monitoring of many human diseases. It is already proving a valuable mechanism in oncology, inflammation, auto-immune diseases, and neurodegenerative diseases.

Dysregulation of histone modifications has been associated with the complex origins of colorectal cancer and pancreatic cancer, suggesting that changes in histone modification patterns detected on circulating nucleosomes could therefore be a source of powerful blood-based biomarkers for early cancer detection. A 2019 report in Pathology Oncology Research into histone modifications in colorectal cancer, stated:

> *"It is evident that epigenetics that affects gene activity and expression has been recognized as a critical role in the carcinogenesis."* [4]

Further scientific studies and data continue to confirm the pivotal role epigenetics and nucleosome testing can play in advancing treatments across human biology and answering the hardest scientific and developmental questions.

Introducing Nucleosomics™

This patented technology detects characteristic changes in nucleosomes that occur from the earliest stages of disease, enabling early detection and a better way to monitor disease progression and the patient's response to treatment.

In many cases, epigenetic changes can be detected before genomic changes and before the diseased cells themselves become abnormal enough to show up in traditional biopsies, and before the first symptoms are felt, thus sparing patients from invasive and uncomfortable tests such as biopsies.

The Nu.Q® Discover program enables drug developers and scientists access to a range of state-of-the-art assays for rapid epigenetic profiling in disease model development, preclinical testing, and clinical studies – from discovery to market ready.

"A lot of standard testing focusses on either parts of the nucleosome, the DNA or protein, and do not examine them holistically," adds Terry Kelly.

> *"Our assays look at modifications in both the DNA and protein, giving a deeper insight and a more complete picture of what is happening at the genomic and cellular level."*

"The Nu.Q® approach is sensitive and rapid and, because it requires small volumes for testing, we can look for more markers and ask a lot more questions, resulting in greater understanding and value for clinical researchers and drug developers.

"Epigenetics generates an understanding that allows us to get better results and interrogate the questions in a different and more complete manner."

Having rapid, sensitive tests can save R&D budgets and schedules, liberating clinical research time and defraying financial constraints. They also allow researchers to explore further upstream into the potential causes of a disease and triggers for its progression.

Epigenetic Intelligence

Two papers published in Epigenomics, and the Open University's Open Research Journal have emphasized the importance of epigenetics in determining both the presence of cancer and its prognosis with levels of circulating nucleosomes providing a treatment response biomarker for advanced hepatocellular carcinoma.

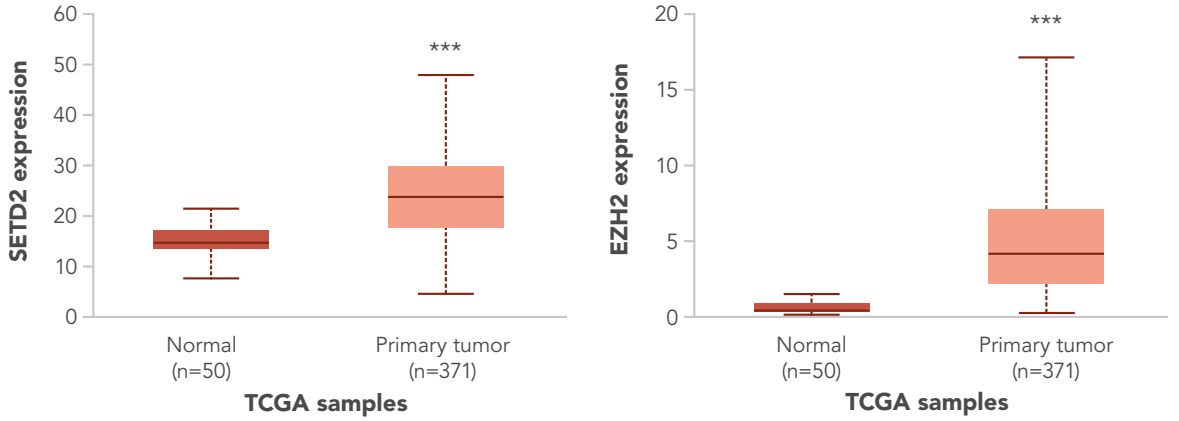
The Epigenomics paper[5], published online in September 2020, illustrated that the histone modifier enhancer of zeste 2 (EZH2) downregulated immune recognition and activation, and upregulated immune checkpoints to create an immunosuppressive tumour microenvironment.

Critical observations have proposed that surviving epithelial cancer cells may acquire immune-suppressive qualities that enable the cancer cells to 'communicate' with immune cells and have an immunoediting influence through the sequential phases of elimination, equilibrium, and escape (*the Three Es*) leading to reduced antigenicity and an immunosuppressive tumour microenvironment.

With EZH2's ability to suppress innate and adaptive immune responses, it indicates the potential value of deploying EZH2 inhibitors in combination with immunotherapies to achieve better responses.

A second Open University paper[6] took this a step further by analysing the role of EZH2 as a driver of sorafenib resistance in patients with advanced hepatocellular carcinoma (HCC) who were being treated with sorafenib. It noted that EZH2 drives this through the epigenetic modification H3K27me3 but that it is counteracted by the enzyme SETD2 and that a higher EZH2/SETD2 ratio predicts a worse prognosis.

EZH2 and SETD2 expression in HCC and normal tissues



***p<0.05

Abbreviations: HCC, hepatocellular carcinoma; PTMs, Post-translational modifications; TCGA, The Cancer Genome Atlas.

References: Salani F et al. Predictive significance of circulating histones in hepatocellular carcinoma patients treated with sorafenib. Epigenomics 2022 14:9, 507-517

These findings were enabled by the ability to test sensitively for circulating nucleosomes and they underscore the opportunities for clinical research to gain deep insights into how drug actions are impacted by epigenetic alterations and how, potentially, to counter and reverse any immunoediting that occurs.

This is particularly pressing in HCC – a disease driven by the interaction between genetic and epigenetic alterations – and the most common type of primary liver cancer. Liver cancer accounts for around 8.3% of cancer deaths worldwide and is a leading cause of cancer deaths in 46 countries, according to figures published in the Journal of Hepatology in October 2022.[7] The number of new cases and deaths of primary liver cancer is predicted to rise by more than 55% by 2040.

Liver cancer rates predicted to rise by 2040

Figures published in the Journal of Hepatology in October 2022.[7]

8.3%

Of cancer deaths worldwide in 2020 were liver cancer

↑ 55%

New cases and deaths predicted by 2040

Its report concluded: *"Liver cancer is a major cause of death in many countries, and the number of people diagnosed with liver cancer is predicted to rise. Efforts to reduce the incidence of preventable liver cancer should be prioritised."*

The Nu.Q® platform and Volition's cutting edge assays, which were used in the sorafenib study[6], offer routes to scientific knowledge that can help direct and strategize research projects.

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The Open University paper reported that the histone H3K27me3/H3K36me3 ratio is a potentially non-invasive predictive biomarker for HCC patients treated with sorafenib, which will allow clinicians to test accurately which patients will respond well to treatment and those who will fail.

SETD2 has been described as an oncosupressor whilst EZH2 overexpression is associated with poor outcomes in liver cancer. The levels of both EZH2 and SETD2 are elevated in liver cancer, reflected by the plasma levels of H3K27Me3 and H3k36Me3 nucleosomes respectively. The ratio of the two Nu.Q® scores was predictive of poor outcome.

"We are at the cutting edge of epigenetic research and Volition is constantly developing its assays and platforms to create understanding that can positively influence drug development and clinical research programmes," adds Terry Kelly. *"Our assays are high quality and are developed with the clinic and the customer in mind and we are continuing to innovate to enable them to look deeply into epigenetics."*

"Epigenetic biomarkers are a valuable tool from target identification to validation in clinical studies and being able to access rapidly and sensitive testing generates transformative results."

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About Volition

Volition is a multinational epigenetics company, powered by Nu.Q®, our proprietary nucleosome quantification platform. Our Nu.Q® Discover program enables drug developers and scientists access to a range of state-of-the-art assays for rapid epigenetic profiling in disease model development, preclinical testing, and clinical studies.

For details go to:
https://volition.com/nu-q-discover

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