the early stages of blood-clot formation – both involve the coordinated condensation of 'sticky biomolecules' (proteins and RNA for stress granules and cellular fragments called platelets for blood clots), albeit at different size scales[9].

Stress granules have been proposed to restrict viral infections[10], but their new-found role in stabilizing lysosomal membranes implicates them in defence against bacterial infection. The bacterium *Mycobacterium tuberculosis*, which causes the disease tuberculosis, damages lysosomes in host cells. This is central to the bacterium's ability to cause disease. In both cell and mouse models, Bussi and colleagues showed that *M. tuberculosis* infection resulted in the formation of lysosome-associated stress granules, which were absent from infections by a mutant *M. tuberculosis* strain with an impaired ability to damage membranes. Disrupting stress granules by G3BP depletion in human immune cells called macrophages greatly enhanced the replication of both types of *M. tuberculosis* strain. Given the key role that stress granules have in protecting against lysosomal damage, it might be expected that individuals with impaired stress-granule response pathways are more susceptible to tuberculosis infection.

Remarkably, the authors show that a previously identified marker[11] for tuberculosis susceptibility is a stress-granule protein that is recruited to stress granules that form near *M. tuberculosis* during infection. Overall, the authors' results simultaneously uncover a new role for stress granules in normal cellular function, and reveal their importance for host–bacterium interactions in the context of one of the world's most pressing global-health problems.

Stephen P. Plassmeyer and **Alex S. Holehouse** are in the Department of Biochemistry and Molecular Biophysics and at the Center for Biomolecular Condensates, Washington University in St. Louis, St. Louis, Missouri 63110, USA.
e-mail: alex.holehouse@wustl.edu

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In retrospect

15 years after a giant leap for cancer genomics

Sheng F. Cai & Ross L. Levine

In 2008, the first comprehensive sequence of a cancer genome was reported, ushering in a new era of molecular diagnostic, prognostic and therapeutic advances informed by an essential framework to understand cancer's complexities.

Efforts to understand the molecular underpinnings of cancer took a giant leap forward fifteen years ago, when Ley *et al.*[1] reported the first complete genome of a cancer – specifically, acute myeloid leukaemia (AML). Genomic data sets of this kind generated in the intervening years have revolutionized our knowledge about tumour biology.

A fundamental understanding of how cancer arises was established in the latter half of the twentieth century by scientists who studied the structures of chromosomes in diseased cells. Their efforts led to the discovery of an anomalous chromosome (termed the Philadelphia chromosome) that is associated with another type of leukaemia, chronic myeloid leukaemia (CML)[2]. This finding was followed by the discovery that this chromosome was formed by a type of exchange of parts of chromosomes called a reciprocal translocation[3]. In the 1990s, it emerged that this translocation generated a cancer-promoting protein called BCR–ABL, which is a fusion of components from two different proteins that forms a type of enzyme called a kinase. The kinase is unusual because it has continuous activity. The finding paved the way for the development and clinical application of a kinase inhibitor called imatinib, which inhibits BCR–ABL-mediated signalling[4]. This demonstrated that potent, specific targeting of a protein arising from a cancer-associated mutation was safe and could achieve durable remissions from cancer[5].

> **"The study by Ley *et al.* was a watershed moment in ushering in the modern era of cancer biology and therapy."**

The success story of CML, once invariably fatal but now a disease that can be well controlled and sometimes eradicated by taking a pill, became an exemplar of precision medicine. At the turn of the twenty-first century, however, the field lacked a clearly defined framework to formulate a similar playbook for other cancers to fuel mechanism-based discovery and drug development.

In 2004, high-throughput sequencing of candidate genes uncovered key cancer 'driver' mutations, including those in the genes *PIK3CA* (ref. 6) and *EGFR* (refs 7,8). This success from a limited number of studies suggested that 'agnostic' studies – ones that do not focus solely on candidate genes but instead explore the entire cancer genome – would transform our understanding of the mutational repertoire of human cancers. In the wake of the Human Genome Project, completed in 2003, whole-genome sequencing of a tumour was within the realm of possibility. But there were considerable challenges to overcome, most notably the costs of sequencing cancer genomes, and the need for analytical tools to identify, at genome scale, somatic mutations (genetic changes that are not heritable because they occur in cells other than eggs or sperm).

It was in this context that Ley and colleagues took up the gauntlet to decode, at single-nucleotide resolution, the entire genome of cancer cells from a person with AML. The effort required a conviction that agnostic mutation discovery had the potential to spur new biological and therapeutic insights about cancer. It also necessitated rigorous foresight to devise analytical workflows that used genomic data derived from the individual's non-tumour cells, taken from the skin, to filter out mutations that were not relevant to the cancer – inherited variants unique to that person (germline polymorphisms) and 'passenger' mutations that occurred in the cancer but were not cancer-causing driver mutations (Fig. 1). Without paired cancer and normal data sets, it would have been impossible to comb through the 3.8 million variants in the cancer genome and identify the ten acquired driver mutations found by Ley *et al.*

The authors also developed a simple but

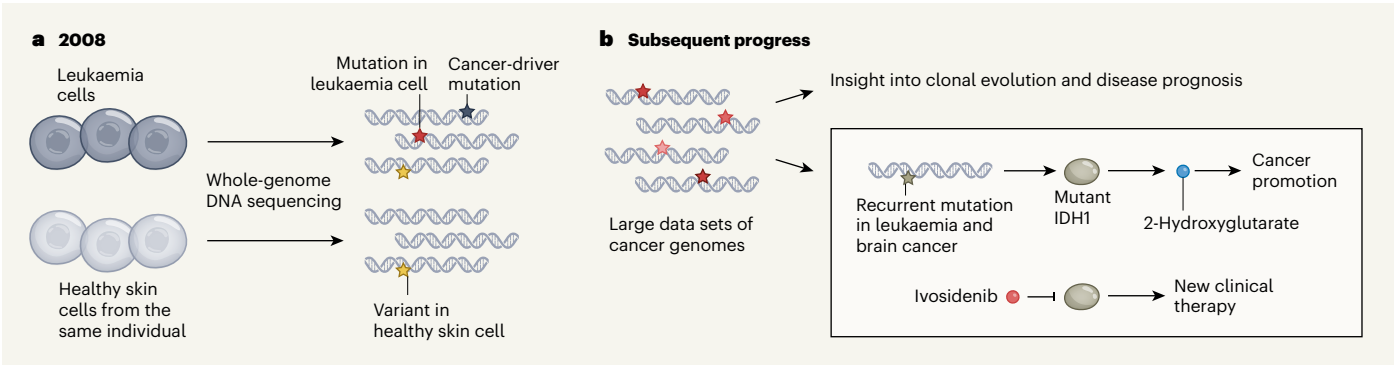

Figure 1 | Fifteen years of cancer genomes. **a**, In 2008, Ley *et al.*[1] presented the first complete sequence of a cancer genome in humans, for a type of leukaemia. By comparing the sequence of the cancer cells with that of non-cancerous skin cells, the authors could distinguish gene variants in healthy skin cells from mutations in leukaemia cells, including genetic changes likely to promote tumours by acting as 'driver' mutations. **b**, The accumulation of cancer genome data in the intervening years has shed light on the mutational changes that occur in a tumour over time and on the evolution of cell lineages (clonal evolution). The data have also revealed mutations that might indicate disease prognosis. Progress has also been made in developing therapies that target newly discovered mutations. For example, a mutation in the gene *IDH1* was found to generate a mutant IDH1 protein that produces the cancer-promoting molecule 2-hydroxyglutarate[17]. This mutant version of IDH1 can be inhibited by the drug ivosidenib, which is used in the clinic to treat leukaemia.

powerful approach to assess the relative frequencies of mutations in an individual's cancer genome that are present in various subpopulations of cancer cells. By leveraging what is called read-count data, they could deduce the frequency of mutant 'reads' at a particular location in the genome and obtain a value called the variant allele frequency (VAF). VAFs enabled inferences to be made about the underlying mutation-associated 'clonal' lineages of cells in a tumour sample that promote therapeutic resistance and disease evolution. These inferences have now been definitively shown to be correct, using single-cell DNA sequencing[9,10]. Studies performed over the past decade demonstrate the power of this technique, providing illustrative cases of clonal evolution under various selection pressures[11,12] and showing the prognostic value of the loss of cells with key mutations (mutational clearance) after therapy[13,14].

Ley and colleagues' seminal report showed that whole cancer genomes could be sequenced, while also making the resounding case that genomes should be sequenced on a much larger scale in the future. The authors wrote that "until hundreds (or perhaps thousands) of normal genomes and other AML tumours are sequenced, the contextual relevance of the mutations found in this [tumour] genome will be unknown".

Notably, a subsequent study by Ley and colleagues, of a larger set of AML genomes, identified recurrent mutations in the *IDH1* gene[15]. This work, coupled with sequencing studies of protein-encoding regions of the genome in brain tumours, identified *IDH1* mutations in a type of brain cancer called a glioma[16]. That research led to mechanistic and therapeutic studies showing how mutant versions of IDH1 and IDH2 proteins produce the cancer-promoting molecule 2-hydroxyglutarate[17]. These mutant proteins can be therapeutically targeted for clinical benefit in AML and in brain tumours[18]. Together these discoveries showed how agnostic studies of cancer genomes can identify previously unknown mutations with prognostic, biological and therapeutic consequences.

With sequencing costs continuing to fall and the growth of collaborative international consortia focused on cancer-genome profiling, the cancer genomics field has identified three million genetic alterations in tens of thousands of human cancer genomes spanning dozens of cancer subtypes, with ever-increasing mechanistic and therapeutic impact. Scientists continue to transition studies of cancer genomes to achieve single-cell resolution, and to investigate comparatively larger groups of clinically annotated samples. As a result, it is expected that much more will be learnt about the mutational processes that promote cancer development, the effect of selective pressures on the evolutionary trajectories of cancer-cell lineages, and how cancer develops as a varied (heterogeneous), multiclonal cellular ecosystem in concert with a dynamic microenvironment. None of this would have been possible without cancer-genome sequencing, and the study by Ley *et al.* was a watershed moment in ushering in the modern era of cancer biology and therapy.

Today, genomic sequencing as part of clinical care has transformed cancer diagnostics, clinical trials and the use of new therapies to improve outcomes for people with cancer. Our unprecedented view of the cancer genome empowers clinicians, computational biologists and bench scientists alike to define biologically relevant groups of people with cancer, direct genomic inquiry and ultimately identify new therapies and biomarkers. It also provides a crucial lens to study and interrogate pre-malignant conditions, in which tissues might contain mosaics of wild-type cells and cells harbouring cancer-associated mutations, and to understand how somatic mutations in non-malignant dividing tissues contribute to an ever-increasing spectrum of human diseases.

As much as scientists have learnt over the past 15 years, there remains so much more to uncover about what makes cancer such a lethal disease and a vexing public-health problem. The path to eradicating it is fraught with challenges, but understanding the genomic landscape has positioned us well to continue to translate discoveries into meaningful benefits for people who have cancer.

Sheng F. Cai and **Ross L. Levine** are in the Department of Medicine, Leukemia Service, and the Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, New York 10065, USA.
e-mails: cais1@mskcc.org; leviner@mskcc.org

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