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Backgrounder

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Secret book of a breast cancer read for the first time

Preamble:

As we grow and develop, our cells divide. With every cell division, the three billion “letters” of DNA that make up our genetic instructions have to be copied. However, we know that the copying process is not always perfect. Mistakes occasionally occur, and sometimes they can’t be repaired. This process gives rise to cells that do not behave as they should – sometimes they die, sometimes they never divide again, and sometimes, if that mutation or “spelling mistake” in the genetic instructions happens in a gene that controls cell division, then the cells grow in an uncontrolled way. This is often how cancer develops.

What cancer researchers haven’t been able to do until now is to find *all* of the mutations present in a given tumour.

What did the research team discover?

For the first time, BC Cancer Agency scientists have decoded the entire genome of a patient’s metastatic breast cancer by sequencing the tumour DNA, and found all of the mutations present in the cancer genome. The results will be published in the international science journal *Nature*, on October 8th 2009.

The team found a total of 32 mutations that alter proteins in the metastatic breast cancer. The team was then able to look back in time and find out how many of these 32 mutations were present in the primary tumour at the time of the original diagnosis, nine years earlier.

Remarkably, only 11 of the 32 mutations were found in the original tumour, implying that considerable evolution takes place within the cancer cells over time, and during and after therapy.

Moreover, of the 11 mutations found in the original primary tumour, only five could have been present in all of the tumour cells. Six mutations were present in only a fraction of the cells. This is a fundamental observation showing mutational heterogeneity – i.e. right from the outset, not all of the cells of the breast cancer contained the same mutations.

Some of the mutations also suggested clues as to the cell processes disrupted when the cancer started.

Why is this discovery groundbreaking?

This is the first time that scientists have been able to identify all of the mutations present in a breast tumour cells obtained directly from a patient. And it is the first time the evolution of a breast tumour has been completely delineated by DNA sequencing. The ability to analyze both the original and the metastatic cancer cells has given us unprecedented information about how breast cancer develops and progresses.

In particular, the discovery that the primary tumour was heterogeneous (not all of the cancer cells had the same mutations) from the start and evolved considerably over time is a very provocative finding that will change the way we think about developing new breast cancer drugs and deciding which patients will benefit the most from which treatments.

How did the research team conduct the study?

It took the international human genome consortium several years and hundreds of millions of dollars to decode the first human genome, the “secret book of humans” in 2001.

The BC Cancer Agency team decoded the breast tumour’s DNA in a matter of weeks and at a fraction of the cost, using the latest “next-generation” DNA sequencing technology.

The team studied two lobular breast cancer tumours from the same patient – the original tumour, and a metastatic, or recurring tumour that was diagnosed nine years later.

They asked a single question: *What is the difference in the DNA sequence between the original, primary tumour and the subsequent metastatic tumour?*

They found 32 “spelling mistakes” or mutations in the DNA sequence encoding the proteins found in the metastatic cancer, and then looked to see how many of those same spelling mistakes were present in the original tumour. This was done by measuring very precisely the number of copies of the normal DNA sequence and the number of copies with the mutation, in the primary tumour.

How was the research made possible?

This discovery is a huge scientific and a philanthropic success story. The research team was led by Samuel Aparicio, the Nan and Lorraine Robertson Chair of Breast Cancer Research based at the BC Cancer Agency and the University of British Columbia, in partnership with his colleague Marco Marra, Director of the Michael Smith Genome Sciences Centre at the BC Cancer Agency.

The work was also made possible by the collaborative contributions of many funding sources. Primary to this effort was the BC Cancer Foundation, through its *Weekend to End Breast Cancer* walk, and the millions of dollars raised by thousands of *Weekend* walkers and donors throughout B.C over the past six years. Also key were contributions from the Canadian Breast Cancer Foundation, BC/Yukon Region, through its support for bioinformatics expertise in the Molecular Oncology department at the BC Cancer Agency.

The next-generation technologies and molecular pathology facility used for the study were supported by the Canadian Institutes for Health Research (CIHR), Genome Canada, Genome BC, the Canada Foundation for Innovation, and the Michael Smith Foundation for Health Research (MSFHR) and the National Cancer Institute, USA. Several trainees on the research team were supported by MSFHR and also by CIHR.

Key to the discoveries was the co-existence of the BC Cancer Agency's cancer clinic and its research teams; the collaboration between clinicians, patients and researchers was crucial.

What was the role of technology in the discovery?

Technology was key; the discovery was made possible by the state-of-the-art, next-generation DNA sequencing technology platform at the BC Cancer Agency's Michael Smith Genome Sciences Centre. The team used this technology to sequence all of the DNA bases in the cancer, over 43 times, to find all of the single-letter spelling mistakes. Every based in the DNA was sequencing several times to guard against errors in the sequencing process.

In 1986 the Nobel Laureate, Renato Dulbecco suggested that cancer biologists would never fully understand cancer, until the entire DNA sequence the genome of cancer cells could be obtained. Within the last two years, next generation sequencing technologies have brought this within reach.

The first DNA sequencing process was discovered by the Nobel Laureate Fred Sanger. Sanger sequencing, as it's generally known, is the method that was used to decode the first human genome and the SARS virus at the BC Cancer Agency Genome Sciences Centre in 2003. However the Sanger methods reached a plateau in efficiency and costs.

In the last two years there's been an enormous leap in DNA sequencing technologies. They differ from previous methods by miniaturizing the sequencing process. This has led to a dramatic increase in capacity and scale, so that we can now obtain the same amount of data from one instrument in a week that took a year and a room full of equipment, eight years ago.

What does this discovery mean for breast cancer patients? How will it affect cancer treatment and diagnosis?

The key finding is that the DNA sequence of a primary breast tumour can be heterogeneous from the start and can evolve significantly. This is a fundamental discovery that impacts the way cancer biologists should consider approaching drug development and targeting of cancers in the future.

Drug discovery researchers have historically assumed that tumours are uniform, with the same mutations in the DNA sequence of all cells. However, we now know that distinct subsets of cells exist within the tumour, right from the beginning. These clones of cells are thought to be responsible for treatment failures, for example by harboring mutations that allow cells to survive treatment with anti-cancer drugs, and then to spread around the body.

The same assumption of tumour uniformity has been used to decide which patients are offered which drugs. However, the "biomarkers" (proteins or mutations) that doctors use to make these decisions may not be present in all cells within the tumour.

This is a wake-up call that the heterogeneity of breast cancers needs to be accounted for at every stage of tackling breast cancer. We now have the genomic tools we need to help researchers develop drugs and biomarkers that take heterogeneity into account.

Next-generation DNA sequencing technology means that researchers can now study the complete genome of an individual patient's cancer tumour much faster. They can determine which mutations make cells resistant to drug therapy, and hence which drugs will be the most effective for that patient's cancer. This advances the development of personalized medicine for cancer patients.

What are the next steps?

The team is now focusing on learning more about the mutations present in distinct subtypes of breast cancer and on building a comprehensive map of breast cancer mutations based on a study of 2000 cancers. They are focusing on sequencing the genomes of a subset of breast cancers that are known to be particularly aggressive, and for which available treatment options do not give very good results. This new project involves sequencing the genomes of several hundred patients' tumours, again using next-generation DNA sequencing technologies. The team is also sequencing the DNA of tumours from patients enrolled in clinical trials, to learn whether mutations can be found that predict sensitivity or resistance to particular drugs.

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Other information sources:

- **BC Cancer Agency information on breast cancer:** <http://www.bccancer.bc.ca/PPI/TypesofCancer/Breast/default.htm>
- BC Cancer Agency Molecular Oncology Department: <http://molonc.bccrc.ca/>
- BC Cancer Agency Genome Sciences Centre (GSC): <http://bcgsc.ca/>
- BC Cancer Agency next-generation sequencing information: http://molonc.bccrc.ca/?page_id=191
- *Nature*: www.nature.com
- NCI (US) General cancer info: <http://www.cancer.gov/> and breast cancer info: <http://www.cancer.gov/cancertopics/types/breast>
- NCIC / Canadian Cancer Society: http://www.cancer.ca/research/?sc_lang=en, with breast cancer info at: http://www.cancer.ca/canada-wide/about%20cancer/types%20of%20cancer/what%20is%20breast%20cancer.aspx?sc_lang=en
- CBCF BC/Yukon Region: <http://www.cbcf.org/en-US/bc%20yukon.aspx>