RESEARCH HIGHLIGHTS

AACR-SU2C RESEARCH ALERTS

ORGANOIDS COULD GUIDE PERSONALIZED THERAPY

TITLE: "Oral mucosal organoids as a potential platform for personalized cancer therapy"
SU2C AUTHOR: Hans Clevers, MD, PhD
GRANT: SU2C-Dutch Cancer Society Tumor Organoids Dream Team
Published: Cancer Discovery, May 3, 2019
DOI: http://dx.doi.org/10.1158/2159-8290.CD-18-1522

Cell culture models called organoids could potentially be used to find the most effective individualized treatment, such as using drugs or radiotherapy, for patients with head and neck cancers.

Summary by the AACR:

Head and neck cancers are difficult to treat, partly because their location in the body makes surgery complicated, and partly because patient response to treatment has been quite variable. In addition, more than half of the patients relapse even after being treated. Thus, there is a need for reliable methods to help identify the most effective treatments for a particular patient.

The Dream Team co-funded by SU2C and the Dutch Cancer Society has been developing 3D cell culture models called organoids for different cancers. In a recent publication in the premier AACR journal *Cancer Discovery,* the team shared its important progress in developing and leveraging head and neck cancer organoids to potentially help guide treatment decisions.

The team grew organoids using surgical resections or biopsies from 31 head and neck cancer patients. They used the genetic information from these organoids to understand why a patient may respond to a particular treatment, or to explore other drugs that may be effective in treating head and neck cancer (even those which are not currently being used to treat this cancer type).

They found that when the organoids had mutations in certain genes – *PIK3CA, KRAS, HRAS* or *BRAF* – the mutations were resistant to cetuximab, a targeted therapy used in many cases. This information may prompt efforts to screen patients for mutations in these genes before treating these patients with cetuximab to avoid unnecessary treatment.

Head and neck cancer patients can be treated with radiation either before or after surgery, sometimes in combination with chemotherapy. The researchers explored the use of organoids to predict response to radiation. They observed positive indications that the response of the organoids to radiation in the laboratory were similar to the corresponding patient's response to radiotherapy. That is, a patient whose organoids were killed by radiation in the laboratory had a lasting response to radiotherapy. In contrast, patients whose organoids were not killed by radiation in the laboratory, did not respond favorably to radiotherapy. These results strongly suggest that organoids can be used to predict whether a particular patient will be responsive to radiation treatment.

In summary, the team led by Dr. Clevers demonstrated the potential of using head and neck cancer organoids in guiding treatment decisions. We look forward to the day when patients can be exposed to treatment regimens with the highest chances of success and the least toxicity.

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NEW DRUG COMBO LOOKS PROMISING IN OVARIAN CANCER

TITLE: "Single-Arm phases 1 and 2 trial of niraparib in combination with pembrolizumab in patients with recurrent platinum-resistant ovarian carcinoma"
DOI: http://dx.doi.org/10.1001/jamaoncol.2019.1048
PUBLISHED: *JAMA Oncology,* June 13, 2019
GRANT: SU2C-Ovarian Cancer Research Alliance (OCRA)-National Ovarian Cancer Coalition (NOCC) Ovarian Cancer Dream Team
SU2C AUTHORS: Alan D. D'Andrea, MD, Dana-Farber Cancer Institute,
Leader, Elizabeth M. Swisher, MD, University of Washington, Co-leader
Ursula A. Matulonis, MD, Dana-Farber Cancer Institute, Investigator
Panagiotis A. Konstantinopoulos, MD, PhD, Dana-Farber Cancer Institute, Young Investigator

Women with ovarian cancer who have chemotherapy but suffer recurrence of the disease have limited options for further treatment. A clinical trial shows that a combination of a powerful immunotherapy drug plus a new drug called a PARP inhibitor has encouraging action in ovarian cancer and may open a new avenue for treatment.

Summary by the AACR:

Women with ovarian cancer usually have surgery to remove the tumor or tumors and then chemotherapy combined with other drugs. The chemotherapy most often involves a platinum-based agent. The disease sometimes becomes resistant to the platinum-based therapy, so if the disease comes back, the patient's treatment options are limited. Thus, finding new treatments could potentially help more women survive the disease.

The SU2C-Ovarian Cancer Research Alliance (OCRA)-National Ovarian Cancer Coalition (NOCC) Ovarian Cancer Dream Team was a major supporter of an important clinical trial that tested a new approach to second-line treatment. The team tried out a combination of niraparib (Zejula) and pembrolizumab (Keytruda), drugs that attack cancer cells in different ways.

Niraparib is what is called a PARP inhibitor – a drug that interferes with the process that allows cells to repair damage to the DNA. If enough damage accumulates, the cancer cells can die. The drug was approved by the FDA in 2016.

Pembrolizumab is one of the best-known immunotherapy drugs. It is a "checkpoint inhibitor " that unleashes the immune system to attack and kill cancer cells.

The researchers enrolled 14 patients (nine patients with ovarian cancer and five patients with triple-negative breast cancer) in the phase 1 trial. Fifty-three patients with ovarian cancer were enrolled

in the phase 2 portion of the trial. The team published its findings on the integrated analysis for phase 1/2 of 60 ovarian cancer patients in the prestigious journal *JAMA Oncology*.

Overall, the drug combination was tolerated by the patients and yielded an overall response rate of 18 percet, including 5 percent complete response, 13 percent partial response, 47 percent with stable disease and 33 percent with progressive disease, which the researchers felt were encouraging responses. However, the patient numbers are small, and the team advocates the need for a larger trial to validate the findings. If confirmed, the drug combination could represent a new therapeutic option for women who need a second-line treatment for ovarian cancer.

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A SOURCE OF RESISTANCE IN COLON CANCER

TITLE: "V211D mutation in MEK1 causes resistance to MEK inhibitors in colon cancer"
SU2C AUTHOR: Rona Yaeger, MD, Memorial Sloan Kettering Cancer Center
GRANT: Stand Up To Cancer Colorectal Cancer Dream Team
Published*: Cancer Discovery,* September 2019
DOI: http://dx.doi.org/10.1158/2159-8290.CD-19-0356

SU2C-supported researchers are actively testing targeted drugs called MEK inhibitors to treat colorectal cancers with mutations in the *BRAF* gene. After identifying a mutation that may keep patients from responding to the drug class, they showed how another type of MEK inhibitor can be used.

Summary by the AACR:

Targeted drugs can be especially effective and less toxic. Because of certain mutations in some colorectal cancers, targeted drugs that block the pro-proliferative MAPK signaling pathway are being actively explored.

Members of the SU2C Colorectal Cancer Dream Team are conducting numerous clinical trials to identify effective treatment strategies for colorectal cancer patients. Rona Yaeger, MD, an investigator on the Dream Team, as part of a clinical trial, is treating colon cancer patients with a MEK inhibitor called binimetinib (MEK is a protein that is part of the MAPK signaling pathway) in combination with another targeted drug, an anti-EGFR antibody, called panitumumab.
In this new paper in AACR's premier journal, *Cancer Discovery*, Yaeger and her team share their important finding that can explain why a colorectal cancer patient progressed even when treated with the MEK inhibitor. They identified a new mutation in the cancer cells of this patient. They proceeded to study in the laboratory other drugs that can be used to kill colorectal cancer cells with such a mutation. Their experiments point to the possibility of treating patients who have become resistant to allosteric MEK inhibitors (such as binimetinib), with a different MEK inhibitor drug type (called ATP-competitive inhibitors).

The efforts of the Dream Team underscore the importance of understanding why patients do not respond to a particular treatment, and how this knowledge can help map out new therapeutic strategies.

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LEAN AND STABLE WEIGHT MAY REDUCE RISK OF MULTIPLE MYELOMA

TITLE: "Elucidating under-studied aspects of the link between obesity and multiple myeloma: Weight pattern, body shape trajectory, and body fat distribution"
SU2C AUTHORS: Catherine Marinac, PhD, Dana-Farber Cancer Institute; and Timothy R. Rebbeck, PhD, Harvard T.H. Chan School of Public Health
SU2C GRANT SU2C Multiple Myeloma Dream Team
PUBLISHED: *JNCI Cancer Spectrum*, June 24, 2019
URL: https://doi.org/10.1093/jncics/pkz044

Maintaining a lean and stable weight throughout life may be of benefit in preventing multiple myeloma.

Summary by the AACR:

Multiple myeloma (MM) is a cancer of the plasma cells that are part of our blood. Obesity has been shown to increase one's risk for developing MM. On the other hand, it has not been clearly shown whether intentionally losing weight or maintaining a specific weight in adulthood can help keep MM at bay.

A team of scientists, including members of the SU2C Multiple Myeloma Dream Team, analyzed weight pattern and multiple myeloma diagnoses data from two famous studies that have followed both female and male health care workers over long periods of time – the Nurses' Health Study, and the Health Professionals Follow-up Study, respectively.

People who had extreme weight cycling – gain and loss of more than 20 pounds – had an increased risk of developing MM when compared to individuals who maintained their weight. In addition, individuals who started with a mid-range body shape and grew larger, had a greater risk of developing MM than those who maintained a lean body shape throughout adulthood.

"Our results suggest that a larger and increasing body shape through age 60 and possibly extreme weight cycling and peripheral adiposity are modifiable risk factors for MM that warrant confirmation in other well-powered prospective studies, " the scientists wrote. "Collectively, our findings support the notion that avoiding weight gain by maintaining a lean and stable weight throughout life, particularly beginning early in life, in keeping with public health recommendations, confers the added benefit of MM prevention."

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AACR-SU2C RESEARCH ALERTS

RESEARCHERS USE "GOT" TO FOCUS ON BLOOD CANCERS

TITLE: "Genotyping of Transcriptomes links somatic mutations and cell identity"
SU2C AUTHOR: Dan A. Landau, MD, PhD
GRANT: Innovative Research Grant 2016
PUBLISHED: *Nature*, July 3, 2019
DOI: http://doi.org/10.1038/s41586-019-1367-0

Scientists integrated genotyping with high-throughput single-cell RNA sequencing to study how mutations can corrupt the formation of blood cells and other blood components and how they contribute to the development of cancers.

Dan A. Landau

"Blood cell development is a complex process whereby stem cells, pass through multiple intermediary stages to give rise to a multitude of mature blood cells, " said Dan A. Landau, MD, PhD, Weill Cornell Medicine, a 2016 recipient of an Innovative Research Grant from SU2C.

"We know that malignant mutations disrupt this process to lead to myeloproliferation, but until now, we were not able to study this in patient samples. Our new technology – GoT – allows for the first time to link somatic mutations and cell identity in tens of thousands of single-cells, so that we can study complex processes like blood development, and understand how it corrupted by somatic mutations. This high-resolution mapping of the two superimposed development trajectories – the normal and malignant – helped identify novel potential therapeutic strategies to correct the malignant progression. More broadly, this method will empower cancer researchers to chart directly in patient samples how mutations interact with the cell identity to drive cancer."

Summary by the AACR:

In cancer research, GoT doesn't stand for "Game of Thrones, " but it's still an epic struggle as scientists try to unlock mysteries such as how mutations in different cell types within a patient can influence the progression of cancer.

Dr. Landau has developed different tools to characterize individual cells in cancer patients. Understanding how individual cells can morph into cancer and change through treatment can open doors to effectively stopping cancer before it develops and preventing treatment relapse.

In this new paper in *Nature*, Landau and a team of researchers developed and used a methodology called GoT (Genotyping of Transcriptomes) to study cells from the bone marrow of patients with a blood cancer called myeloproliferative neoplasms. With GoT, they found that the impact of a particular mutation is not the same across all types of blood cells. The use of GoT enabled them to

delineate the importance of multiple mutations in imparting cancerous characteristics to a particular cell.

The software that they used to analyze their GoT data was dubbed “IronThrone.”

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CAR-T CELLS ARMED TO ATTACK GLIOBLASTOMA

TITLE: "CAR-T cells secreting BiTEs circumvent antigen escape without detectable toxicity"
SU2C AUTHORS: Marcela V. Maus, MD, PhD
SU2C GRANT: Stand Up To Cancer Innovative Research Grant
PUBLISHED: *Nature Biotechnology***,** July 22, 2019
URL: https://www.nature.com/articles/s41587-019-0192-1

Although CAR-T cells have shown exceptional promise in treatment of blood cancers, they have not been effectively deployed against glioblastoma. Arming CAR T cells with the capability to secrete antibodies called specific bispecific T cell engagers (BiTEs) was shown to significantly increase the anti-glioblastoma efficacy of these cells.

Summary by the AACR:

Marcela V. Maus

Tooling up the patient's own immune cells, in a treatment strategy called CAR T cell therapy, has significantly improved outcomes for blood cancer patients. Unfortunately, the same treatment strategy has not been as successful in treating glioblastoma, the deadliest form of brain cancer. Marcela V. Maus, MD, PhD, of Massachusetts General Hospital and Harvard Medical School, and the recipient of an SU2C Innovative Research grant, is working on giving CAR T cells a bigger arsenal with which to fight brain cancer.

CAR T cells are usually designed to home in on a particular protein on the surface of cancer cells. The problem is that a cancer cell may or may not have the protein that the CAR T cell is targeting. Dr. Maus had previously tested a CAR T cell that targeted the mutant form of a cell surface protein called EGFR. When her team tested this CAR T cell in patients, they saw that cells that did not have the mutant protein persisted after the treatment.

In this new paper in the journal *Nature Biotechnology*, Maus and her research group describe how they beefed up the CAR T cells by arming them with the ability to secrete antibodies called bispecific T-cell engagers or BiTEs. These BiTEs can enable the T-cells to kill cancer cells that don't have the mutant protein. Not only did the BiTEs synergize with the CAR T cells, but they also activated other T cells which were not originally targeted to the cancer cells.

Laboratory experiments in mice showed that the BiTE-secreting CAR T cells were able to effectively eradicate glioblastoma. These results have the potential of paving the way for treating patients with these BiTE-secreting CAR T cells.

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THE "STOP APPETITE" HORMONE MAY ALSO STOP CANCER

TITLE: "Oncolytic viruses engineered to enforce leptin expression, reprogram tumor-infiltrating T cell metabolism, and promote tumor clearance"
SU2C Author: Greg M. Delgoffe, PhD
SU2C Grant: Innovative Research Grant (IRG)
Published: *Immunity***,** Aug. 27, 2019
DOI: https://doi.org/10.1016/j.immuni.2019.07.003

Immunotherapy can be improved to help fight cancer. One strategy is to stimulate T cells by using a hormone that usually signals the brain that the body has had enough to eat.

Summary by the AACR:

There has been great excitement in seeing that our body's defense system called the immune system can be mobilized to kill cancer cells. Unfortunately, the immune cells, especially the cancer-killing T cells, are sometimes incapacitated by metabolic abnormalities.

Greg M. Delgoffe

Greg M. Delgoffe, PhD, is an assistant professor in the University of Pittsburgh Department of Immunology and a 2016 recipient of a Stand Up To Cancer Innovative Research Grant (IRG). In a paper published recently in the journal *Immunity,* he has helped demonstrate how resolving these metabolic abnormalities can mobilize T cells against cancers like melanoma and pancreatic cancer.

The key to unlocking the potential of T cells is in a hormone called leptin, which normally has a totally different function in the body. It's produced by fat cells, and it communicates to the brain that the body has enough stored fat. Basically, it tells your body when it's time to quit eating. Unfortunately, leptin, as a hormone, cannot be simply taken by patients as a pill. It isn't even effective when injected directly into the tumor. A different delivery system may be in order – such as an oncolytic virus.

This is a type of virus that attacks tumor cells specifically and leaves normal cells alone. When enough of them get into a tumor cell, they can cause it to disintegrate. Bioengineering the virus to secrete leptin is like a double whammy against cancer. The viruses themselves can kill cancer cells. In addition, the leptin that the virus secretes reprograms the metabolism of T cells and enables these immune cells also to attack the cancer cells.

When Delgoffe's team conducted laboratory experiments, the scientists saw that oncolytic viruses by themselves were quite effective in slowing down tumor growth. But oncolytic viruses that were bioengineered to produce leptin were significantly more effective, especially against more aggressive tumors.

These results point to the potential therapeutic benefit of beefing up oncolytic viruses to make them even more effective treatment agents. An oncolytic virus, T-VEC, is already FDA-approved to treat metastatic melanoma. Thus, the work of Delgoffe's team could help lead to additional treatments.