How Do Chloroquines Kill Cancer? New Answers from Penn Research

Anti-malaria drugs known as chloroquines have been repurposed to treat cancer for decades, but until now no one knew exactly what the chloroquines were targeting when they attack a tumor. Now, researchers from the Abramson Cancer Center of the University of Pennsylvania say they have identified that target – an enzyme called PPT1 – opening up a new pathway for potential cancer treatments.

The team also used CRISPR/Cas9 gene editing to remove PPT1 from cancer cells in the lab and found that eliminating it slows tumor growth. They detailed a potent chloroquine developed at Penn, known as DC661, that can take advantage of this new treatment pathway. Their findings were published in Cancer Discovery last week.

“The discovery of this target is critical because chloroquines are currently being evaluated in clinical trials all over the world, including here at Penn, and this knowledge fundamentally changes the way we look at those trials,” said the study’s co-senior author Ravi K. Amaravadi, MD, an associate professor of Hematology-Oncology in the Perelman School of Medicine at the University of Pennsylvania and member of the ACC’s Cancer Therapeutics Program.

Jeffrey D. Winkler, PhD, the Merriam Professor of Chemistry in the School of Arts and Sciences at the University of Pennsylvania and a member of the ACC’s Radiobiology and Imaging Program, was the other co-senior author.

PPT1 is an enzyme which controls both the mechanistic target of rapamycin (mTOR), a major regulator of growth in cancer cells, as well as a process called autophagy, a built-in resistance mechanism which allows cells to survive when under attack by breaking down unneeded parts and recycling them to stay alive. In a previous study, Penn researchers showed these two processes work hand-in-hand, as autophagy provides the nutrients that allow mTOR to direct growth, while mTOR shuts off autophagy when the nutrients aren’t needed. Building off their previous work, researchers used CRISPR/Cas9 to knockout PPT1 from cancer cells to see if its removal had the same effect as a chloroquine.

“The edited cells look like they’ve been treated with a drug, and they grow significantly slower than the unedited cells,” Amaravadi said. “We also compiled data from existing databases and found PPT1 is both highly expressed in most cancers and also associated with poor outcomes.”

Researchers further proved the concept by targeting melanoma cells with DC661, which specifically targets PPT1 and produces cell death in many cell lines tested both in vitro and in vivo. It is a dimeric form of the antimalarial drug quinacrine – meaning it has two molecules of quinacrine bound together with a special linker.

“Our previous studies the chemistry of these compounds is crucial to specifically targeting PPT1, and we used that knowledge to create a potent form of the drug that we’ve now shown is more effective at slowing the growth of cancer cells in mice than the monomeric chloroquines currently under study in clinical trials,” Winkler said.

The co-lead authors were Vito W. Rebecca, PhD, a postdoctoral researcher in Amaravadi’s lab at the time of the research, and Michael C. Nicastri, PhD, who was a graduate student in Winkler’s lab at the time of the work.

Amaravadi said when you put the pieces together, it shows incredible promise.

“We now have a specific molecular target in cancer, as well as a potent way to reach it,” Amaravadi said. “It not only provides new context for current clinical trials involving hydroxychloroquine, but also, with further development of these compounds toward clinical drug candidates, it opens the door for head-to-head testing of our compounds or their optimized derivatives versus current chloroquines to see which is more effective.”

Source: Penn Medicine Communications

Journal Article: Rebecca VW et al. PPT1 promotes tumor growth and is the molecular target of chloroquine derivatives in cancer. Cancer Discovery 2018 Nov 15. Published online.
Seminars and So Forth

Monday 11/19/18 11:00 am
Microbiology Faculty Candidate Seminar
“CAR T cells for Cancer Therapy: Grand Challenges and Opportunities on the Road to Clinical Success.”
Joseph Fraietta, PhD, Director, Solid Tumor Immunotherapy Laboratory, Center for Cellular Immunotherapies, PSOM
JMB Class of ‘62 Auditorium

Monday 11/19/18 12:00 pm
Path and Lab Grand Rounds
“Mapping of the bone marrow microenvironment at single cell resolution.” Iannis Aifantis, PhD, Professor and Chair, Department of Pathology, NYU Langone Medical Center
CRB Austrian Auditorium

Tuesday 11/20/18 2:00 pm
Special Seminar @ CHOP by Fluidigm
“Comprehensively characterize the tumor microenvironment in spatial context with Imaging Mass Cytometry.” Overview of the Hyperion Imaging System.
CTR 4040 (CHOP)

Tuesday 11/27/18 12:00 pm
Distinguished Lecture in Cancer Research
“Of mice and men: Learning about human prostate cancer by using mouse models.” Cory T. Abate-Shen, PhD, Michael and Stella Chernow Professor of Urologic Sciences; Professor of Pathology and Cell Biology, Herbert Irving Comprehensive Cancer Center, Columbia University
Wistar Institute, Caplan Auditorium

Tuesday 11/27/18 3:00 pm
Cancer Biology Special Seminar
“Keep calm and eat on: How phagocytes smell, taste, and ingest their apoptotic meal.” Justin S. A. Perry, PhD, Postdoctoral Fellow, University of Virginia School of Medicine
CRB Austrian Auditorium

Tuesday 11/27/18 4:00 pm
CHOP CCCR Seminar Series
“APOBEC3A: A good defense that comes with a high cost, and potential vulnerability for cancer cells.”
Matthew D. Weitzman, PhD, Professor of Pathology & Laboratory Medicine and Microbiology; Co-Chief, Division of Protective Immunity, Children’s Hospital of Philadelphia
CTR 1200B (CHOP)

Wednesday 11/28/18 12:00 pm
CT3N Work In Progress
Michael J. Mitchell, PhD, Skirkanich Assistant Professor of Innovation, Department of Bioengineering, University of Pennsylvania
SCTR 10-100

Wednesday 11/28/18 4:00 pm
CVI Seminar Series
“Genetic Studies of Human Hematopoiesis.” Vijay Sankaran, MD, PhD, Assistant Professor of Pediatrics, Harvard Medical School, Division of Hematology/Oncology, Boston Children’s Hospital, Associate Member, Broad Institute of MIT and Harvard
SCTR 11-114

Thursday 11/29/18 12:00 am
Radiation Oncology Seminar Series
“Translating Cancer Biology into Novel Therapies.”
Dan Theodorescu, MD, PhD, Paul A. Bunn, Jr. Endowed Chair in Cancer Research; Professor of Surgery and Pharmacology; Director, University of Colorado Comprehensive Cancer Center
SCTR 8-146AB

Thursday 11/29/18 4:00 pm
Otorhinolaryngology-Head and Neck Surgery/ Cancer Biology Guest Speaker
“Novel Mechanisms of PI3K Signaling in Cancer.”
Jennifer Spangle, PhD, Instructor of Pathology, Dana-Farber Cancer Institute and Harvard Medical School
JMB Reunion Auditorium

Friday 11/30/18 12:00 pm
IFI-ACC Research in Progress Seminar
Golnaz Vahedi, PhD, Assistant Professor of Genetics, PSOM
BRB II/III Gaulton Auditorium
Funding Opportunities

RFA-CA-19-005/RFA-CA-19-006
Immunology Science for Cancer Control (NCI P50)

LOI Due Date: January 11, 2019
Application Due Date: February 11, 2019

These FOAs are associated with the Beau Biden Cancer Moonshot℠ Initiative that is intended to accelerate cancer research. Their purpose is to support P50 Developing and Advanced Centers for the study of cancer control implementation science.

Developing Centers will build research capacity to study high priority areas of cancer control implementation science, build implementation laboratories, improve the state of measurement and methods, and improve the adoption, implementation, and sustainment of evidence-based cancer control interventions.

Advanced Centers will study high priority areas of cancer control implementation science, build implementation laboratories, improve the state of measurement and methods, and improve the adoption, implementation, and sustainment of evidence-based cancer control interventions.


NIH Immuno-Oncology Translation Network (IOTN)

These FOAs are associated with the Beau Biden Cancer Moonshot℠ Initiative that is intended to accelerate cancer research. Specifically, this FOA targets the following area designated as scientific priority by the Blue Ribbon Panel (BRP): Recommendation B. Create a translational science network devoted exclusively to immunotherapy approaches to treat and prevent adult cancers.

There are several associated opportunities. LOIs are due in early December; applications are due in early January. Click links for details.

RFA-CA-19-012, UG3/UH3 Phase Innovation Awards Cooperative Agreement
RFA-CA-19-013, U54 Specialized Center – Cooperative Agreements
RFA-CA-19-014, U01 Research Project – Cooperative Agreements
RFA-CA-19-015, U01 Research Project – Cooperative Agreements

NIH Immuno-Oncology Translation Network (IOTN)

These FOAs are associated with the Beau Biden Cancer Moonshot℠ Initiative that is intended to accelerate cancer research. Specifically, this FOA targets the following area designated as scientific priority by the Blue Ribbon Panel (BRP): Recommendation B. Create a translational science network devoted exclusively to immunotherapy approaches to treat and prevent adult cancers.

There are several associated opportunities. LOIs are due in early December; applications are due in early January. Click links for details.

RFA-CA-19-012, UG3/UH3 Phase Innovation Awards Cooperative Agreement
RFA-CA-19-013, U54 Specialized Center – Cooperative Agreements
RFA-CA-19-014, U01 Research Project – Cooperative Agreements
RFA-CA-19-015, U01 Research Project – Cooperative Agreements

RFA-CA-19-012, UG3/UH3 Phase Innovation Awards Cooperative Agreement
RFA-CA-19-013, U54 Specialized Center – Cooperative Agreements
RFA-CA-19-014, U01 Research Project – Cooperative Agreements
RFA-CA-19-015, U01 Research Project – Cooperative Agreements

NIH Immuno-Oncology Translation Network (IOTN)

These FOAs are associated with the Beau Biden Cancer Moonshot℠ Initiative that is intended to accelerate cancer research. Specifically, this FOA targets the following area designated as scientific priority by the Blue Ribbon Panel (BRP): Recommendation B. Create a translational science network devoted exclusively to immunotherapy approaches to treat and prevent adult cancers.

There are several associated opportunities. LOIs are due in early December; applications are due in early January. Click links for details.

RFA-CA-19-012, UG3/UH3 Phase Innovation Awards Cooperative Agreement
RFA-CA-19-013, U54 Specialized Center – Cooperative Agreements
RFA-CA-19-014, U01 Research Project – Cooperative Agreements
RFA-CA-19-015, U01 Research Project – Cooperative Agreements

NIH Immuno-Oncology Translation Network (IOTN)

These FOAs are associated with the Beau Biden Cancer Moonshot℠ Initiative that is intended to accelerate cancer research. Specifically, this FOA targets the following area designated as scientific priority by the Blue Ribbon Panel (BRP): Recommendation B. Create a translational science network devoted exclusively to immunotherapy approaches to treat and prevent adult cancers.

There are several associated opportunities. LOIs are due in early December; applications are due in early January. Click links for details.

RFA-CA-19-012, UG3/UH3 Phase Innovation Awards Cooperative Agreement
RFA-CA-19-013, U54 Specialized Center – Cooperative Agreements
RFA-CA-19-014, U01 Research Project – Cooperative Agreements
RFA-CA-19-015, U01 Research Project – Cooperative Agreements

NIH Immuno-Oncology Translation Network (IOTN)

These FOAs are associated with the Beau Biden Cancer Moonshot℠ Initiative that is intended to accelerate cancer research. Specifically, this FOA targets the following area designated as scientific priority by the Blue Ribbon Panel (BRP): Recommendation B. Create a translational science network devoted exclusively to immunotherapy approaches to treat and prevent adult cancers.

There are several associated opportunities. LOIs are due in early December; applications are due in early January. Click links for details.

RFA-CA-19-012, UG3/UH3 Phase Innovation Awards Cooperative Agreement
RFA-CA-19-013, U54 Specialized Center – Cooperative Agreements
RFA-CA-19-014, U01 Research Project – Cooperative Agreements
RFA-CA-19-015, U01 Research Project – Cooperative Agreements

NIH Immuno-Oncology Translation Network (IOTN)

These FOAs are associated with the Beau Biden Cancer Moonshot℠ Initiative that is intended to accelerate cancer research. Specifically, this FOA targets the following area designated as scientific priority by the Blue Ribbon Panel (BRP): Recommendation B. Create a translational science network devoted exclusively to immunotherapy approaches to treat and prevent adult cancers.

There are several associated opportunities. LOIs are due in early December; applications are due in early January. Click links for details.

RFA-CA-19-012, UG3/UH3 Phase Innovation Awards Cooperative Agreement
RFA-CA-19-013, U54 Specialized Center – Cooperative Agreements
RFA-CA-19-014, U01 Research Project – Cooperative Agreements
RFA-CA-19-015, U01 Research Project – Cooperative Agreements

NIH Immuno-Oncology Translation Network (IOTN)

These FOAs are associated with the Beau Biden Cancer Moonshot℠ Initiative that is intended to accelerate cancer research. Specifically, this FOA targets the following area designated as scientific priority by the Blue Ribbon Panel (BRP): Recommendation B. Create a translational science network devoted exclusively to immunotherapy approaches to treat and prevent adult cancers.

There are several associated opportunities. LOIs are due in early December; applications are due in early January. Click links for details.

RFA-CA-19-012, UG3/UH3 Phase Innovation Awards Cooperative Agreement
RFA-CA-19-013, U54 Specialized Center – Cooperative Agreements
RFA-CA-19-014, U01 Research Project – Cooperative Agreements
RFA-CA-19-015, U01 Research Project – Cooperative Agreements

NIH Immuno-Oncology Translation Network (IOTN)

These FOAs are associated with the Beau Biden Cancer Moonshot℠ Initiative that is intended to accelerate cancer research. Specifically, this FOA targets the following area designated as scientific priority by the Blue Ribbon Panel (BRP): Recommendation B. Create a translational science network devoted exclusively to immunotherapy approaches to treat and prevent adult cancers.

There are several associated opportunities. LOIs are due in early December; applications are due in early January. Click links for details.

RFA-CA-19-012, UG3/UH3 Phase Innovation Awards Cooperative Agreement
RFA-CA-19-013, U54 Specialized Center – Cooperative Agreements
RFA-CA-19-014, U01 Research Project – Cooperative Agreements
RFA-CA-19-015, U01 Research Project – Cooperative Agreements

NIH Immuno-Oncology Translation Network (IOTN)

These FOAs are associated with the Beau Biden Cancer Moonshot℠ Initiative that is intended to accelerate cancer research. Specifically, this FOA targets the following area designated as scientific priority by the Blue Ribbon Panel (BRP): Recommendation B. Create a translational science network devoted exclusively to immunotherapy approaches to treat and prevent adult cancers.

There are several associated opportunities. LOIs are due in early December; applications are due in early January. Click links for details.

RFA-CA-19-012, UG3/UH3 Phase Innovation Awards Cooperative Agreement
RFA-CA-19-013, U54 Specialized Center – Cooperative Agreements
RFA-CA-19-014, U01 Research Project – Cooperative Agreements
RFA-CA-19-015, U01 Research Project – Cooperative Agreements

NIH Immuno-Oncology Translation Network (IOTN)

These FOAs are associated with the Beau Biden Cancer Moonshot℠ Initiative that is intended to accelerate cancer research. Specifically, this FOA targets the following area designated as scientific priority by the Blue Ribbon Panel (BRP): Recommendation B. Create a translational science network devoted exclusively to immunotherapy approaches to treat and prevent adult cancers.

There are several associated opportunities. LOIs are due in early December; applications are due in early January. Click links for details.

RFA-CA-19-012, UG3/UH3 Phase Innovation Awards Cooperative Agreement
RFA-CA-19-013, U54 Specialized Center – Cooperative Agreements
RFA-CA-19-014, U01 Research Project – Cooperative Agreements
RFA-CA-19-015, U01 Research Project – Cooperative Agreements