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Journal of Blood & Lymph
Review in 3 weeks Publishing in 72 hours Open Access
ISSN: 2165-7831

Preethi Ravindranathan
UT Southwestern Medical Center
5323 Harry Hines Blvd, JA5.130D
Dallas TX 75390
Ph: 214-648-3363/3764

Research Focus: Prostate cancer

- Designing and evaluating small molecules to inhibit protein interactions to block prostate cancer progression
- Studying the role of variants of AR protein in advanced stages (castration -resistant) of prostate cancer (CRPC) and evaluating rationally designed peptidomimetics in blocking AR variant activity
- Development of tumor culture model for the evaluation of therapeutic agents in human solid tumors

Areas of interest

Prostate cancer
Small molecule drugs
Peptidomimetics
Androgen Receptor
Breast cancer
Molecular endocrinology

SHORT BIO

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Employment History

Research Associate
May 2014-Present
UT Southwestern Medical Center, Dallas TX

Research Technician II
Jun 2014-May 2014
UT Dallas, Dallas, TX
(Site of activity: UT Southwestern Medical Center, Dallas TX)

Research Technician II
Dec 2008-Apr 2011
UT Southwestern Medical Center, Dallas TX

Graduate Research Assistant
Aug 2006-Oct 2008
UT Health Science Center at Tyler, Tyler TX

Intern
Dec 2005-May 2006
Central Leather Research Institute, Chennai, India

Member Affiliations

- American Association for Cancer Research (AACR)
- Society for Basic Urologic Research (SBUR)

Education

Master of Science (Biotechnology)
Aug 2006-Oct 2008
Stephen F. Austin State University, Nacogdoches, TX

Bachelor of Technology (Industrial Biotechnology)
May 2002-Jun 2006
Anna University, Chennai, India

- **Recipient of Gold Medal** for securing 8th position among 607 candidates who graduated with Bachelor of Technology (Industrial Biotechnology) degree in Apr 2006 from Anna University, India

SHORT BIO

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JOURNAL ARTICLES

Key publications

- **Peptidomimetic targeting of critical androgen receptor-coregulator interactions in prostate cancer**; Preethi Ravindranathan, Tae-Kyung Lee, Lin Yang, Margaret Centenera, Lisa Butler, Wayne Tilley, Jer-Tsong Hsieh, Jung-Mo Ahn, Ganesh Raj; **Nature Communications**, May 2013, 4:1923
- **Central role for PELP1 in non-androgenic activation of androgen receptor in prostate cancer**; Lin Yang, Preethi Ravindranathan, Payal Kapoor, Meera Raman, Ganesh Raj; **Molecular Endocrinology**, April 2012, 26(4):550 –561
- **Dual roles of PARP-1 promote cancer growth and progression**; Matthew Shiewer, Jonathan Goodwin, Sumin Han, Chad Brenner, Michael Augello, Jeffry Dean, Fengzhi Liu, Jamie Planck, Preethi Ravindranathan, Arul Chinnaiyan, Peter McCue, Leonard Gomella, Ganesh Raj, Adam Dicker, Jonathan Brody, John Pascal, Margaret Centenera, Lisa Butler, Wayne Tilley, Felix Feng, Karen Knudsen; **Cancer Discovery**, December 2012, 2(12):1134-49
- **Progesterone receptor-B enhances estrogen responsiveness of breast cancer cells via scaffolding PELP1- and estrogen receptor-containing transcription complex**; Andrea Daniel, Angela Gaviglio, Todd Knutson, Julie Ostrander, Preethi Ravindranathan, Yan Peng, Ganesh Raj, Douglas Yee, Carol Lange; **Oncogene** , advance online publication January 2014, DOI: 10.1038
- **Ablation of the oncogenic transcription factor ERG by Deubiquitinase inhibition in prostate cancer**; Shan Wang, Rahul Kollipara, Nishi Srivastava, Rui Li, Preethi Ravindranathan, Elizabeth Hernandez, Eva Freeman, Caroline Humphries, Payal Kapur, Yair Lotan, Ladan Fazli, Martin Gleave, Stephen Plymate, Ganesh Raj, Jer-Tsong Hsieh, Ralf Kittler; **PNAS**, March 2014, 111(11):4251-6
- **The social network of PELP1 and its implications in breast and prostate cancer (a review)**; Vijay Gonugunta, Lu Miao, Sareddy Reddy, Preethi Ravindranathan, Ratna Vadlamudi, Ganesh Raj; **Endocrine Related Cancer,** May 2014, 21(4):T79-T86

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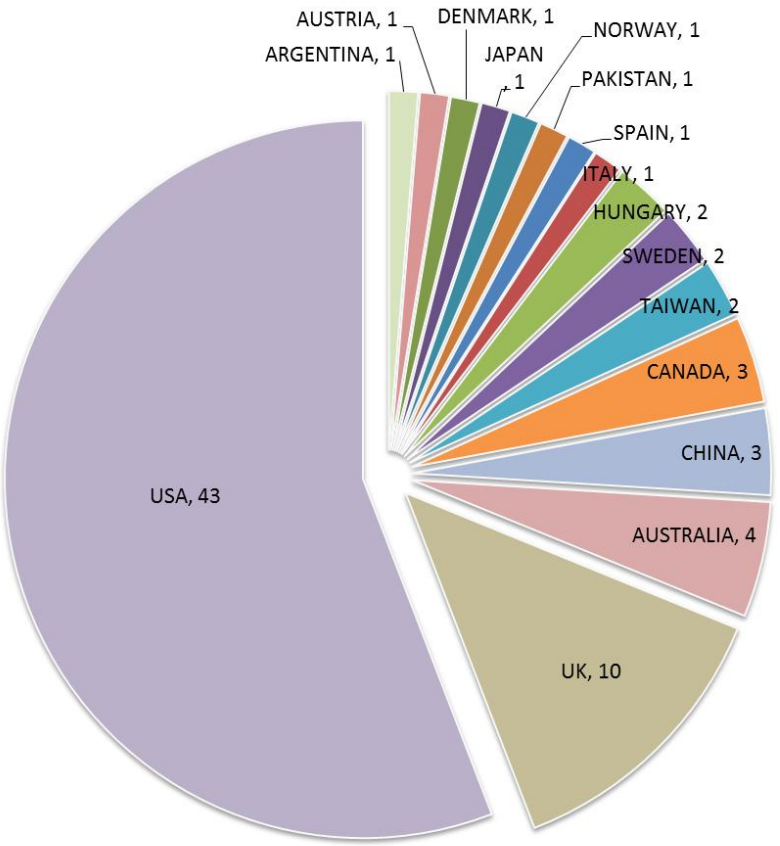
Research referred by researchers from all over the world*



WORLDWIDE IMPACT

*Based on country of citing of corresponding author

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Mainstream-media coverage of research work

Picked up by 6 news outlets:

WebMD

THE HINDU Today's Paper » NATIONAL » TAMIL NADU

City woman's research work featured in Nature

M. Dinesh Varma

Her ideas could contribute to prostrate cancer treatment in future

Preethi Ravindranathan

Chennai researcher Preethi Ravindranathan's work on a tiny molecule that could result in a better remedy for prostate cancer has been featured in the latest issue of Nature Communications.

The 27-year-old researcher was the youngest in the research group at UT Southwestern Medical Center in Dallas where she enrolled in 2009.

The collaborative effort, led by Dr. Ganesh V. Raj, involved researchers Tae-Kyung Lee, Lin Yang, Margaret M. Centenera, Lisa Butler, Wayne D. Tilley, Jer-Tsong Hsieh and Jung-Mo Ahn.

Preethi's contribution to the project involves conducting molecular biology and biochemical experiments, data analyses and in manuscript writing.

Expressing delight over the outcome of her work, Ms. Preethi told *The Hindu* in an e-mail response that she had always had a fascination for fighting prostate cancer through research.

"Designing small molecules to disrupt essential protein interactions in prostate cancer has always appealed to the engineer in me," she said.

The paper that was published in Nature Communications, a weekly peer-reviewed scientific journal published by the Nature Publishing Group, involved a small molecule, called D2, which was designed by the group to mimic the interaction surface between androgen receptor (AR), a key player in prostate cancer, and a few select proteins that participate in prostate cancer signalling.

"The principal advantages of using such small molecules is that while they can be made to target specific protein interactions, and hence minimise non-target effects by not affecting other protein interactions, which may be essential for the normal functioning of cells, they can be easily taken up by cells owing to their small size," Ms. Preethi said.

Though the new molecule (drug) was non-toxic in mouse and human tissue models, further tests were required before such targeting of prostate cancer could move on to Phase 1 clinical trials involving human participants.

Worldwide, prostate cancer is considered to be the second most frequently diagnosed cancer of men and the fifth most common cancer overall. In India, though prostate cancer prevalence is lower compared to the West the concerns here are more over recent upward trending of the disease and poorer survival rates.

Ms. Preethi is an alumnus of the Rajalakshmi Engineering College where she completed her Engineering (B.Tech) degree in Biotechnology with a gold medal.

She then completed a Master's in biotechnology from the University of Texas Health Science Centre, Tyler in the US.

Her parents, Ravidranathan and Vasanta, too were motivating and supportive. "They inculcated in me a deep sense of enjoyment in learning and experimenting at an early age and made my science and math textbooks come alive," Ms. Preethi said.

Article Link: http://www.webmd.com/prostate-cancer/news/20130531/experimental-drugs-show-promise-against-prostate-cancer

Prostate Cancer Health Center

Listen

Experimental Drugs Show Promise Against Prostate Cancer

Tumor growth suppressed in lab tests; human trials still needed, study authors say

WebMD News from HealthDay

By Mary Elizabeth Dallas

HealthDay Reporter

FRIDAY, May 31 (HealthDay News) -- Researchers have identified a new class of drugs that show promise for treating advanced prostate cancer. The drugs, known as peptidomimetics, interfere with the signaling necessary for prostate cancer cells to grow, according to a new study.

Prostate cancer depends upon the actions of androgens, such as the hormone testosterone. Androgens activate androgen receptors, resulting in a signal that causes prostate cancer cells to grow.

To stop tumor growth, men with prostate cancer have been treated with drugs to block the production of androgens or block the receptor where androgens bind. However, tumors can grow despite this treatment because of mutations in androgens or receptors.

In the latest study, published online May 28 in *Nature Communications*, a team of researchers led by Dr. Ganesh Raj, associate professor of urology at UT Southwestern Medical Center at Dallas, found the nontoxic peptidomimetic agents could disrupt androgen-receptor signaling and prevent tumor growth.

When tested in mouse and human tissue models, the drugs blocked the activity of androgens by attacking the protein in a different spot from where the androgen binds, the researchers explained. As a result, prostate cancer cells do not receive the signal to grow -- even when the androgen receptor is activated.

"We are hopeful that this novel class of drugs will shut down androgen-receptor signaling and lead to added options and increased longevity for men with advanced prostate cancer," Raj, the study's senior author, noted in a university news release.

One expert was optimistic about the new findings.

"The study represents a significant step forward in the development of a new molecular targeted therapy for advanced prostate cancer," said Dr. Manish Vira, director of the Fellowship Program in Urologic Oncology at North Shore-LIJ's Arthur Smith Institute for Urology in Lake Success, N.Y.

He said the new drug works at "preventing the [cell] receptor from promoting cancer cell growth signaling," and added that "the study is proof in principle that rationale design of peptidomimetics can lead to the development of a new class of anti-cancer therapy."

The researchers noted more testing is needed before the drugs could progress to clinical trials involving humans. Results obtained in laboratory experiments are not always replicated in humans.

"Most drugs now available to treat advanced prostate cancer improve survival rates by three or four months," Raj added. "Our new agents may offer hope for men who fail with the current drugs."

MEDIA ATTENTION

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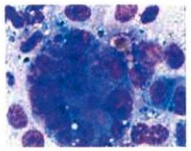
C. Mainstream-media coverage of research work

ecancer

Researchers identify novel class of drugs for prostate cancers

29 May 2013



A new study on prostate cancer describes a novel class of drugs developed by UT Southwestern Medical Center researchers that interrupts critical signaling needed for prostate cancer cells to grow.

In men with advanced prostate cancer, growth of cancer cells depends on androgen receptor signaling, which is driven by androgens, such as testosterone.

To thwart tumour growth, most patients with advanced prostate cancer receive drugs that block the production of androgen or block the receptor where the androgen binds.

Unfortunately, such treatments invariably fail and patients die of prostate cancer with their androgen receptor signaling still active and still promoting tumour growth.

In the new study, available in *Nature Communications*, a team of researchers led by Dr. Ganesh Raj, associate professor of urology at UT Southwestern, found that they could disrupt androgen receptor signaling using a novel class of drugs called peptidomimetics.

This therapeutic agent consists of an engineered small protein-like chain designed to mimic peptides that are critical for androgen receptor function. The peptidomimetic agents block the activity of the androgen receptor even in the presence of androgen by attacking the protein in a different spot from where the androgen binds.

"We are hopeful that this novel class of drugs will shut down androgen receptor signaling and lead to added options and increased longevity for men with advanced prostate cancer," said Dr. Raj, the senior author of the study.

Dr. Raj compared the action that takes place to a lock and key mechanism. In prostate cancer, the androgen receptor (lock) is activated by the androgen (key) resulting in a signal that causes prostate cancer proliferation.

In advanced prostate cancer, despite drugs targeting either the lock (androgen receptor) or the key (androgen production), there can be aberrant keys that open the lock or mutated locks that are always open, resulting in cancer cell proliferation. Instead of trying to block the lock or the key, peptidomimetics uncouple the lock and key mechanism from the proliferation signal.

Thus, even with the androgen receptor activated, the prostate cancer cells do not receive the signal to proliferate and do not grow.

The researchers tested their drug in mouse and human tissue models. The novel drug proved non-toxic and prevented androgen receptor signaling in cancer cells. The response is highly promising and suggests that peptidomimetic targeting of prostate cancer may be a viable therapeutic approach for men with advanced disease.

Further testing is needed before a drug could move to Phase 1 clinical trials that involve human participants.

"Most drugs now available to treat advanced prostate cancer improve survival rates by three or four months," Dr. Raj said. "Our new agents may offer hope for men who fail with the current drugs."

These findings represent the development of a first-in-class agent targeting critical interactions between proteins. Other cellular and disease processes eventually could also be targeted with peptidomimetics, the scientists said.

Medical Xpress
medicalxpress.com

Home Cancer May 28, 2013

Small molecule could have big impact on cancer

Dr. Jung-Mo Ahn, associate professor of chemistry at The University of Texas at Dallas, has designed and synthesized a novel small molecule that might become a large weapon in the fight against prostate cancer.

In a study published online May 28 in the journal *Nature Communications*, Ahn and his colleagues at UT Southwestern Medical Center describe the rational design of the molecule, as well as laboratory tests that show its effectiveness at blocking the cancer-promoting function of proteins called androgen receptors.

Androgen receptors are found inside cells and have complex surfaces with multiple "docking points" where various proteins can bind to the receptor. Each docking point has a unique shape, so only a correctly shaped molecule will fit.

Androgen hormones, such as testosterone, are the primary molecules that bind to androgen receptors. Such binding sets off a chain of events that activates several different processes in the human body, including stimulating the development and maintenance of male characteristics.

Looking for a new approach to battle prostate cancer, Ahn and his colleagues keyed in on blocking a critical docking point on the androgen receptor.

"When a tumor is trying to grow, activation of this location provides what the tumor needs," Ahn said. "There are other surfaces on the androgen receptor that are free to continue working with their respective proteins and to continue functioning. We sought to block only one set of interactions that contribute to prostate cancer growth. That's why we thought our approach might lead to potent efficacy with fewer side effects."

Using computer-assisted molecular modeling, Ahn designed a helix-mimicking small molecule that fits precisely into a pocket on the androgen receptor that is associated with prostate cancer. Collaborating with senior study author Dr. Ganesh Raj, associate professor of urology at UT Southwestern and a specialist in treating urologic cancers, the researchers tested the compound in animal and isolated human tissue. Without exhibiting noticeable toxicity, the compound prevented the androgen receptor from recruiting its protein partners and it blocked the growth of prostate cancer cells.

"We have shown that our molecule binds very tightly, targeting the androgen receptor with very high affinity," Ahn said. "We also have confirmed that it inhibits androgen function in these cells, which is a promising finding for drug development. We showed that it does work through these mechanisms, and it is as effective in inhibiting the proliferation of prostate cancer cells as other compounds currently in clinical trials."

Ahn plans to continue his research to better understand how the small molecule and related compounds he developed work against cancer on a molecular level. He said much work is left to do before any potential drugs or treatment might be developed, but added "this is an exciting start."

About 239,000 men are expected to be diagnosed with prostate cancer in the U.S. in 2013 and about 30,000 will die of the disease, according to the American Cancer Society.

Journal reference: Nature Communications

Provided by University of Texas at Dallas

4.3 /5 (4 votes)

Featured

Medical

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C. Mainstream-media coverage of research work

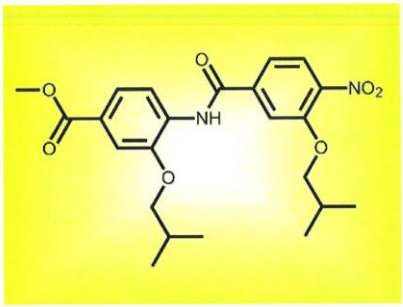
Europe

EurekAlert!

Preventing Dangerous Liaisons

Author: Melania Tesio
Published: 18 June 2013

Source / Publisher: Nature Communications/Nature Publishing Group



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The growth of advanced prostate cancer depends on the androgen receptor (AR). Following binding to the male hormone testosterone and to its metabolite 5α-dihydrotestosterone, AR interacts with its cofactor PELP1 (proline, glutamic acid, and leucin protein 1). By this it promots the transcription of genes involved in cellular proliferation.

Preethi Ravindranathan, University of Texas Southwestern Medical Center at Dallas, USA, and colleagues designed a peptidomimetic – a small protein-like chain designed to mimic a peptide – that blocks AR activation by preventing its binding to PELP1. This novel molecule called D2 (pictured) acts by mimicking the LXXLL motif, a PELP1 sequence which is crucial for its binding to AR.

When tested in an animal model, D2 blocked the androgen-dependent growth of prostate tumors. This compound may, therefore, constitute a novel pharmacological tool to treat advanced prostate cancers.

Peptidomimetic targeting of critical androgen receptor-coregulator interactions in prostate cancer.
P. Ravindranathan, T. K. Lee, L. Yang, M. M. Centenera, L. Butler, W. D. Tilley, J. T. Hsieh, J. M. Ahn, G. V. Raj,
Nat. Commun. **2013**, *4*, 1923.
DOI: 10.1038/ncomms2912

Public release date: 28-May-2013

Contact: Amanda Siegfried
amanda.siegfried@utdallas.edu
972-883-4335
University of Texas at Dallas

Small molecule could have big impact on cancer

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- Second international conference on Hematology and blood Disorders.

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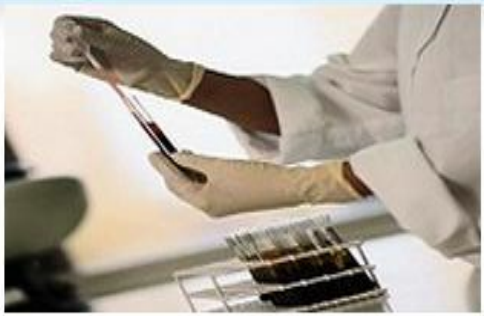

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