

Concept-to-Clinic

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Experimental Therapeutics Launches First New GSBS Program in 10 Years

The Experimental Therapeutics Academic Program enrolled 11 students for its inaugural academic school year that began with the fall 2010 semester.

As the first new program offered at The University of Texas Graduate School of Biomedical Sciences at Houston (GSBS) in more than 10 years, the Experimental Therapeutics Academic Program (ETAP), which received formal approval from the Texas Higher Education Coordinating Board (THECB) in March 2010, trains students in every aspect of therapeutics as a discipline.

More than five years ago, **Varsha Gandhi, Ph.D.**, professor in Experimental Therapeutics and director of ETAP, and several colleagues, identified the need for a program to focus solely on the discipline of therapeutics. Programs existed in cancer biology, immunology, and virology and gene therapy, but nothing specifically addressed the many phases of therapeutics. A pharmacology tract is available in the Cell and Regulatory Biology Program – but that deals only with a drug and its metabolites. So in collaboration with steering committee members and direction from GSBS Dean George M. Stancel, Ph.D., Gandhi conceptualized the program, designed its curriculum and courses, wrote the program proposal and presented it to the six GSBS Standing Committees and the GSBS Executive Committee. Next, the MD Anderson and UTHealth provosts signed off on the proposal and submitted it to the THECB for formal approval.

“If there is no research in therapeutics, patients will have

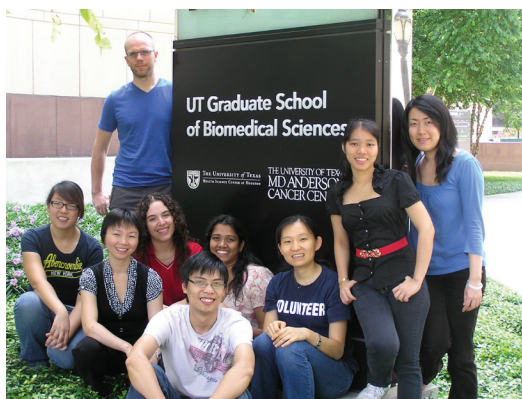
limited options in the future,” says Gandhi. Investigators in the rapidly growing field of therapeutics have an understanding of the pathophysiology and biology of a disease; know mechanisms for identification of targets; have experience in how to chemically create a drug; and are keen to move therapeutic agents all the way through to the clinic. Therefore, as more cancer drugs gain approval from the Food and Drug Administration each year and graduates look to the pharmaceutical industry for careers, she believed that starting a

therapeutics program now was the perfect time to increase the number of scientists in the field and enable research to continue.

The program offers students two tracks of study – an M.S. and a Ph.D. program. Both tracks require “Ethical Dimensions of the Biomedical Sciences” and “Principles of Therapeutics” courses. In the “Principles of Therapeutics” course, students receive a broad overview of therapeutics and its history, primarily focused on cancer but applicable to any disease; learn different diseases for which therapeutics were developed; and learn how therapeutics

are created from a chemical molecule and how to make a drug. Candidates in the M.S. program must complete a minimum of 30 credit hours and Ph.D. candidates must fulfill a minimum of 54 credit hours.

Basic science through clinical and translational research is covered in the program, including chemistry, disease biology, drug development and mechanisms of action. Students learn to apply the scientific method of hypothesis testing to research projects
(continued on page 4)



GSBS, DoCM Faculty honor Gandhi

Varsha Gandhi, Ph.D., professor in Experimental Therapeutics, was elected to serve as faculty president at The University of Texas Graduate School of Biomedical Sciences at Houston for the 2010-2011 academic year.

Responsibilities include serving on the executive committee, chairing biannual faculty meetings and presenting a commencement address.

Gandhi also received the **Gerald P. Bodey Award for Excellence in Education**



at the Division of Cancer Medicine’s Fourth Annual Faculty Recognition and Awards Program held Dec. 15, 2009.

Nominated by Garth Powis, D.Phil., professor and chair in Experimental Therapeutics, Gandhi’s contributions include establishing a mentor program for departmental junior faculty; organizing a postdoctoral fellow career development forum; didactic teaching; supervising graduate students; and developing the new Experimental Therapeutics Academic Program at GSBS.

George M. Stancel, Ph.D., professor and dean at GSBS, and Lisa Chen, Ph.D., instructor in Experimental Therapeutics and a mentee of Gandhi, supported her nomination.



Congratulations to **Riccardo Spizzo, M.D., Ph.D.**, research investigator in Experimental Therapeutics, recipient of the Citation for Excellence in Laboratory Research at the Division of Cancer Medicine's Annual Employee Recognition and Awards Program held Tuesday, May 11, 2010.

Nominated by George A. Calin, M.D., Ph.D., associate professor in Experimental Therapeutics,

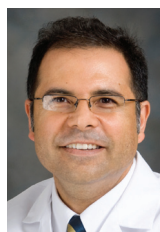
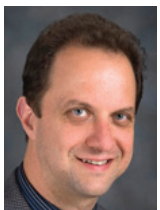
Spizzo's contributions range from serving as the primary liaison for more than 10 projects with collaborators from around the world to teaching various techniques regarding non-coding RNAs and microRNAs to others in the laboratory.

Scientifically speaking, Spizzo identified a regulatory network that includes the tumor suppressor microRNA 145, the tumor suppressor TP53 and the estrogen receptor alpha in breast cancers. The clinical implications of this finding will impact the selection of patients to receive microRNAs-based cancer gene therapy. Additionally, Spizzo is the first author on four manuscripts published in the last two years and his nomination was supported not only by his co-workers in the laboratory but by a visiting assistant professor and collaborators from Italy and the Netherlands.

Julie Izzo, M.D., associate professor in Experimental Therapeutics, was appointed an independent expert for the European Commission – Research Directorate General. She serves as an evaluator for the Seventh Framework Programme, which is the primary tool for the European Union to fund research in Europe.



George A. Calin, M.D., Ph.D., associate professor in Experimental Therapeutics, was invited to become a member of the National Institutes of Health Center for Scientific Review's (CSR) Cancer Biomarkers Study Section. His term began July 1, 2010 and ends June 30, 2014.



Bulent Ozpolat, M.D., Ph.D., assistant professor in Experimental Therapeutics, received a 2009 Norman Hackerman Advanced Research Program grant from the Texas Higher Education Coordinating Board (THECB).

Ozpolat's proposal, "A New Approach to Co-Therapy for Breast Cancer," earned funding in the amount of \$99,360.00 beginning Aug. 1, 2010 and ending July 31, 2012. This project seeks to establish the mode of action of CAMK-III, a promising lead inhibitor, and investigate its efficacy as a co-therapy in animal models.

Of 2,387 pre-proposals, 95 were funded and Ozpolat's proposal was one of only two awarded to MD Anderson. According to the THECB, the Norman Hackerman Advanced Research Program is a competitive peer-reviewed grant program created in 1987 to encourage and provide support to faculty members and students in Texas institutions of higher education, both public and independent, to conduct basic research.

Promotions

Congratulations on a job well done!

The following ET employees were recently promoted: **Mena Abdelmelek** to research assistant II for Dr. Taly Spivak-Kroizman; **Kumudha Balakrishnan, Ph.D.**, to assistant professor in Dr. Varsha Gandhi's laboratory; **Ryan Graham** to research assistant II for Dr. Geoffrey Bartholomeusz; **Brian James, Ph.D.**, to senior research scientist, and **Anshuman Sewda** to research technician II – both in Dr. Garth Powis' laboratory; and **Shujun Shentu** to senior research assistant for Dr. Christine Stellrecht.

People Notes

The Department of Experimental Therapeutics continues to grow by leaps and bounds. Please welcome the following new (and returning) faces:

Name	Position	Laboratory PI
Burcu Aslan	Research Assistant I	Ozpolat
Nilza Marie Biaggi-Labiosa	Postdoctoral Fellow	Lopez-Berestein
Xuebo Chen	Senior Research Assistant	Mehta
Kirk Culotta, Pharm.D.	Assistant Professor	Pharmaceutical Development Center
Justin Jacob	Research Assistant I	Bartholomeusz
Jiankang Jin, Ph.D.	Research Scientist	Robertson
Takayuki Kato, Ph.D.	Postdoctoral Fellow	Priebe
Santosh Kumar, Ph.D.	Postdoctoral Fellow	Mehta
Cheng-Chan Lu, Ph.D.	Visiting Professor	Calin
Timothy Palculict	Senior Research Assistant	Powis
Sharangdhar Shivanand Phatak	Graduate Research Assistant	Zhang
Rachel Marie Raia	Graduate Research Assistant	Calin
Tetsuro Setoyama, Ph.D.	Visiting Scientist	Calin
Sheng Sun	Graduate Research Assistant	Darnay/Kuang
Jinsong Wei	Research Assistant II	C. Liu
Moishia Wright	Research Assistant II	Robertson
Seong woo Yoon, Ph.D.	Visiting Associate Professor	Aggarwal

On a related note ... **Diana Victoria Martin, Ph.D.**, in the Translational Chemistry Core Facility, made the switch to research laboratory manager from postdoctoral fellow.

* Please refer to Lotus Notes for telephone numbers and office/lab locations.

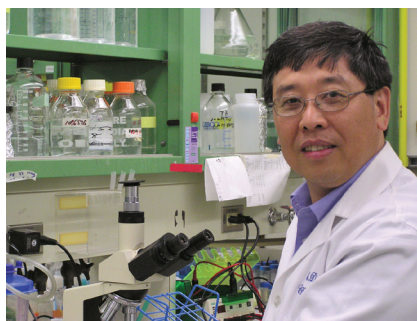
Recombinant Antibody Technology Creates Potential for Novel Therapeutics

Laboratory: Zhen Fan, M.D.

What does Zhen Fan have in common with a benchtop cell bioreactor, you ask? Why, the ability to produce recombinant antibodies, of course!

Fan's expertise lies in cancer biology – specifically the epidermal growth factor receptor (EGFR) family of signaling pathways – and innovative recombinant antibody technology for developing novel antibodies with the potential to become new anti-cancer drugs. As such, he is in the midst of a research project for a High Impact/High Risk Research Award from the Cancer Prevention and Research Institute of Texas (CPRIT) titled, “Development of a novel anti-EGFR antibody-protamine recombinant protein for *in vivo* delivery of small interfering RNAs for cancer therapy.”

A principal investigator in Experimental Therapeutics, Fan is leading a research group that utilizes DNA recombinant technology to engineer genes of antibody-based therapeutic proteins that do not exist naturally. These man-made recombinant antibodies are created by cloning or combining different



genes – or parts of genes – to rationally design novel multifunctional antibodies specifically for therapeutic use. Recombinant antibody technology has many advantages, such as fusing antibodies with proteins that can potentially be used as drugs as Fan proposes in his CPRIT research. He utilizes a three-liter benchtop fermentor and bioreactor (BioFlo®/CelliGen® 115) to produce the antibodies that will carry small interfering RNAs (siRNA) to targeted cancer cells. This bioreactor is the same type as pharmaceutical companies use, only on a smaller scale.

To begin, Fan designs a DNA construct by combining a piece of antibody and a protein

of interest that are introduced to genetically clean host cells (typically Chinese hamster ovary cells), not cancer cells, that are screened for the best cell clones to produce the desired antibody. Once the clone cells are fully characterized, they are adapted from attached cells to suspension cells, which can take up to several weeks or months. At this point, the cells are adapted to a specialized serum-free medium and placed in the bioreactor to grow and secrete antibodies into the medium. After seven to 10 days the batch is complete, cells are discarded and the resulting antibodies are purified and ready to undergo *in vitro* and *in vivo* testing in mice.

Fan's vision is to develop second or third generation of antibodies that will overcome resistance to the first generation antibodies currently used in the clinics by utilizing cutting-edge technology and innovative strategies to produce novel recombinant therapeutic antibodies.

Under the Microscope is a feature highlighting individual laboratories in the Department of Experimental Therapeutics.

In the Pipeline

PDC Plays Integral Role in Nanoparticle Delivery System for Metastatic Melanoma

The Pharmaceutical Development Center (PDC), in collaboration with Elizabeth A. Grimm, Ph.D., professor, and other colleagues in Experimental Therapeutics, aided the development of a novel, liposomal nanoparticle delivery system, DOTAP:cholesterol (DOTAP:Chol), for the melanoma differentiation associated gene-7/ Interleukin-24 (MDA-7/IL-24) by testing the product for intravenous administration and providing guidance for an Investigational New Drug Application (IND).

Melanoma is a systemic disease that requires systemic treatment. However, the current delivery methods for genes such as MDA-7/IL-24 by viral vectors (e.g., adenoviruses or retroviruses) are inefficient and hampered by the induction of anti-vector immunity. Grimm expects the delivery of MDA-7/IL-24 via this liposomal nanoparticle system will result in systemic and local protein production at sites of particle uptake concluding with melanoma growth control.

MDA-7/IL-24 is referred to as the “magic bullet” of cancer immunotherapy because of its dual function as a tumor suppressor and

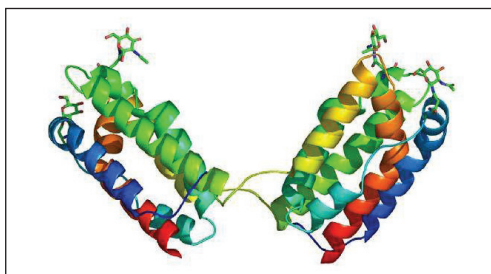


Figure 1. Representation of IL-24 as a potential dimer.

Figure 1. Reference

MDA-7/IL-24 is a unique cytokine—tumor suppressor in the IL-10 family.

Chada S, Sutton RB, Ekmekcioglu S, Ellerhorst J, Mumm JB, Leitner WW, Yang HY, Sahin AA, Hunt KK, Fuson KL, Poindexter N, Roth JA, Ramesh R, Grimm EA, Mhashilkar AM. *Int Immunopharmacol.* 2004 May;4(5):649-67. Review.

a pro-inflammatory cytokine. The hypothesis supposes that systemic delivery of IL-24 through DOTAP:Chol to melanoma patients will inhibit tumor growth and complement existing treatments because MDA-7/IL-24 first was identified as a melanocyte-derived tumor suppressor whose expression is lost during the development of invasive primary melanoma.

Grimm and colleagues demonstrated that MDA-7/IL-24 was expressed by melanocytes both *in vitro* and *in vivo* and showed a loss of expression as primary cutaneous tumors invade the dermis. Treatment with MDA-7/IL-24 inhibits melanoma cell growth and induces apoptosis *in vitro*. These *in vitro* studies, as well as Phase I and II adenoviral delivered gene therapy trials, of MDA-7/IL-24 provided proof-of-principle that restoration of the MDA-7/IL-24 gene into melanoma “in transit” lesions, concurrent with protein production and apoptosis at the tumor site, can be achieved with little or no toxicity.

The DOTAP:cholesterol nanoparticle is a novel, extruded, liposome-like particle used successfully *in vivo* and one of the best formulations with respect to balancing toxicity and *in vivo* nucleic acid transfer efficiency. Cationic lipids are a preferred component for nucleic acid delivery due to the high efficiency of nucleic acid transfer associated with these lipid formulations and this technique forms a lipid bilayer encapsulating the condensed DNA. Previous studies demonstrated that improved, (continued on page 4)

Introducing...



Name: Kellie Garrett-Ekeland

Title: Operations Manager

Departmental Role: Provide support for ET administration and faculty members

Birthplace: Ooooooklahoma! Where the wind comes sweepin' down the plains ...

The word that best describes me is: Inquisitive

My proudest accomplishment is: Workwise, I established the finance department for Texas A&M University, College of Engineering, Qatar campus.

People who know me would say: "KK, how are you?"

When not working for a living: Sailing, gardening, studying and hugging grandbabies – not necessarily in that order...

My heroes and/or heroines include: My Dad. I lost him too early to prostate cancer. As a child, I thought it was his profile on the dime.

Favorite movie: "Monsters Inc."

Favorite book: "Earth Abides" by George R. Stewart

The most unique thing about me is: I am Native American of the Cherokee tribe.

Favorite quote: "I saw the angel in the marble and carved until I set him free." – Michelangelo

Favorite song(s): "Tomorrow" by Silverchair and "Rooster" by Alice in Chains

What I like most about Houston: Arts, Food, and the Texas Medical Center

What I like least about Houston: It's the largest city in Texas – what's not to like?

Something most people don't know about me: I rode horses to school and had a pet lamb.

ETAP

(continued from page 1)

that include identifying mechanisms of actions of novel agents, testing in preclinical laboratories and mouse models, and validating preclinical efforts in the clinic – the classic "bench-to-bedside" approach. The program also brings together like-minded faculty interested in developing therapeutics but who are not necessarily in the same department or institution. ETAP faculty are chosen based on their diversity of research expertise and represent more than 20 different departments, institutes or centers affiliated with The University of Texas System.

Students completing either degree program have a diversity of career opportunities available to them such as academic research, technology discovery and intellectual property protection or positions within the FDA. Choosing the academic route enables graduates to pursue the development of therapeutics and the identification of targets; create molecules as chemists; analyze and test molecules as biologists; or bring therapeutics to clinical trial as clinical or translational researchers. Industry careers offer positions within the pharmaceutical and biotechnology industries, the FDA or in the area of patent law.

Gandhi hopes that establishing the Experimental Therapeutics Academic Program generates increased interest in learning more about the pathophysiology of cancers, developing and optimizing therapeutics, and providing novel agents and strategies for the clinic. "When a program flourishes, it brings faculty together for intellectual interactions and collaborations," says Gandhi. "In turn, this brings out the best our discipline has to offer for faculty, students and, ultimately, patients."

For more information on ETAP, please visit the program site.

PDC

(continued from page 3)

extruded DOTAP:Chol nanoparticles (100 to 200 nm in diameter) efficiently delivered therapeutic tumor suppressor genes in experimental models of disseminated metastases.

Grimm's next step utilizes DOTAP:Chol nanoparticle delivery of the MDA-7/IL-24 gene to achieve systemic delivery of this tumor suppressor in metastatic melanoma patients. The PDC conducted single dose studies of DOTAP:Chol MDA-7/IL-24 in mice to identify end organ toxicity and its reversibility and established the no-observed-adverse-effect-level. The results will be used to design the dose and schedule for subsequent multiple dose studies conducted in animal models and support progression toward the planned Phase I dose escalation clinical trial of DOTAP:Chol MDA-7/IL-24 in Stage IV metastatic melanoma patients.

Concept-to-Clinic is a publication of the Department of Experimental Therapeutics at The University of Texas MD Anderson Cancer Center.

Published quarterly, we welcome submissions from members of the department and reserve the right to edit for length and style.

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