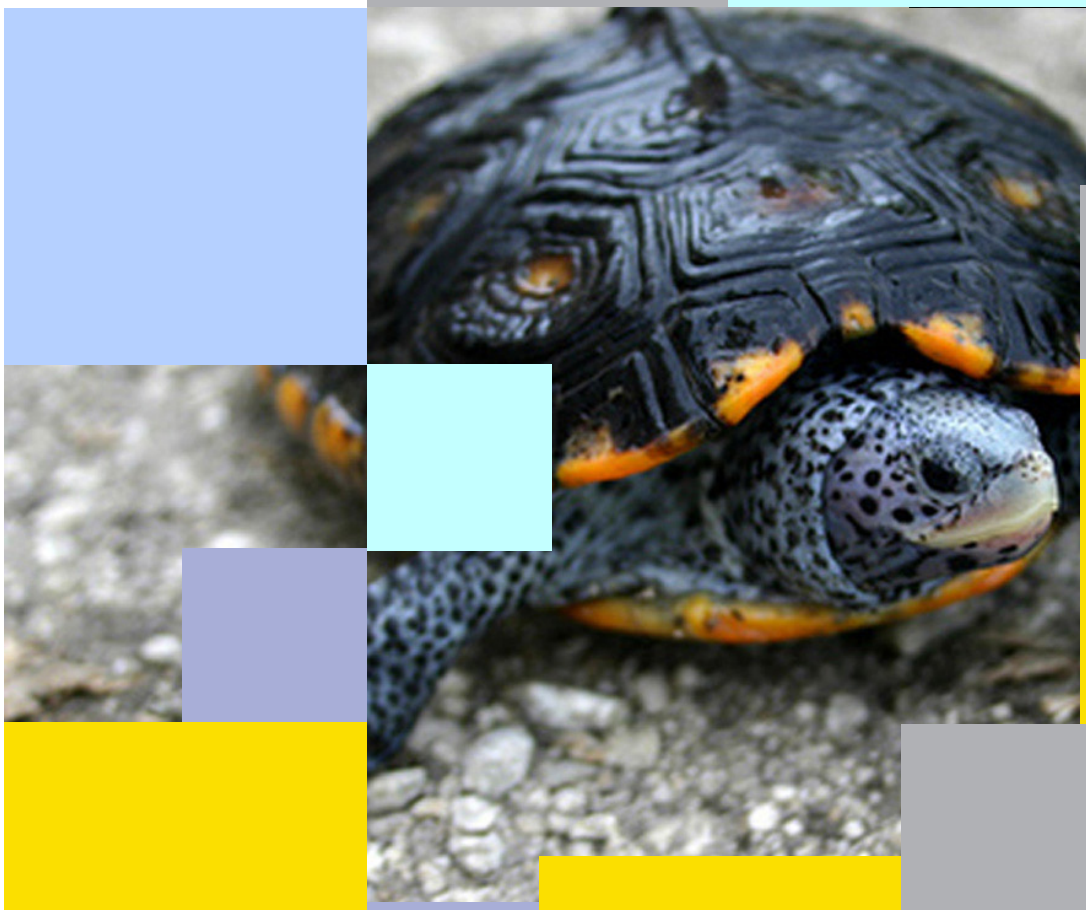
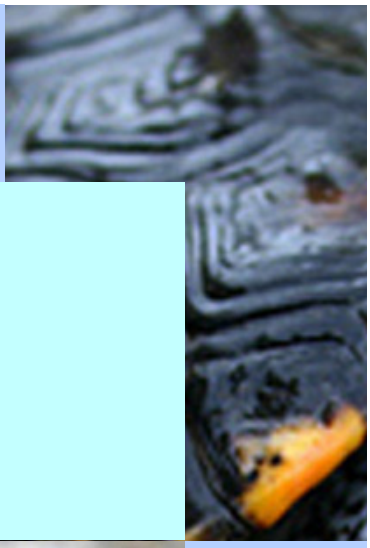
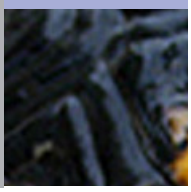
SCIENTIFIC TERRAPIN

VOLUME II
ISSUE II







THE UNIVERSITY OF MARYLAND'S
UNDERGRADUATE RESEARCH JOURNAL

SCIENTIFIC TERRAPIN

SPRING 2011

VOLUME II ISSUE II

STAFF LIST 2011

Co-Presidents/Editors-in-Chief
Baijia Jiang
Jasjeet Khural

Applied Sciences Managing Editors
Ann Sun
Chris Dextras

Applied Sciences Junior Editors
Maia Werbos
Yasmin Kadry

Life Sciences Section Editors
Adam Pampori
George Hao

Life Sciences Junior Editors
Krzysztof Franaszek
Jason Albanese
Allison Dennis

News/Features Section Editor
Kathy Jee

Copy Editor
Niklas Berry

Graphics Chairs
Kelsey Marotta
Jaimie Mertz

Graphics Staff
Elaine Lin
Emily Jones

Webmaster
Emily Jones

Secretary
Rosie Zhang

Treasurer
Nalin Dayal

Faculty Advisor
Dr. Kaci Thompson

MISSION STATEMENT

The University of Maryland, College Park is emerging as a top national research university. It is consistently named as one of the top fifty research universities and one of the top twenty-five public research universities in the nation. The university garnered $401 million dollars in research money in 2008, funding faculty and graduate investigation of our world from the myriad perspectives of scientists, sociologists, businesspeople, historians, and artists.

However, for the University to fully reach its potential as a top research institution, we believe that undergraduate students should play a more central role in the discussion, exchange, and visibility of research on campus. Currently many undergraduate students complete Honors Theses, Gemstone Theses and conduct research in labs on campus. Before now, though, there have been few outlets for students to share their work with the rest of the community and engage in the academic discussion and debate across specialties that sharing of research confers. It is this very "culture of research" that we wish to promote. *Scientific Terrapin* salutes student researchers for their initiative, their dedication, and their pursuit of knowledge and, thus, will fill this void by offering an outlet for student researchers to publish their work across all disciplines, including:

* The Life Sciences – biology, chemistry, biochemistry, and ecology
* The Applied Sciences – engineering, mathematics, computer science, physics, and geology
* The Social Sciences – economics, government and politics, psychology, business, and sociology

Scientific Terrapin provides a stepping stone for scientists across disciplines at the beginning of their research careers. We seek to provide undergraduate researchers a forum to present their work and receive peer and faculty review, as well as readership and recognition. We seek to connect student researchers with one another, so they might form intellectual partnerships and friendships, and so will sponsor workshops and presentations to not only encourage inter-disciplinary discussion and debate, but to share research opportunities and practical advice for advancement in their fields. We herald the work of promising young minds and extraordinary mentors, allowing the community to learn about exciting research produced at the University of Maryland. And last, we hope to inspire students as they enter the university or continue with their education, to take the next step and join their fellow classmates in contributing to this culture of research and to claim their integral role in the vibrant and dynamic research at the University of Maryland.

CALL FOR SUBMISSIONS

We will be accepting submissions on a rolling basis with priority consideration for those who submit by September 15 for the Fall 2011 issue. We encourage you to submit your work with a faculty mentor on campus, your findings from an internship, or an abridged Honors thesis or Gemstone paper in a scientific research article. The journal is accepting articles in the fields of life sciences, social sciences, and applied sciences. Submission details and guidelines can be found on our web site, www.scientificterrapin.umd.edu.

Scientific Terrapin models our review process after professional journals. It is designed in a manner to provide authors rigorous and valuable criticism to help them learn about the scientific writing process and to improve the quality of their analysis. Upon submission of a manuscript, a qualified student editorial staff conducts an initial peer review. Components such as quality of analysis, scope of work, and quality of writing are evaluated. The manuscript is then returned to the author with a request for revisions. Revised manuscripts are then shared with University of Maryland faculty members in the field of the work in review. Faculty members evaluate the quality of the work and its contribution to the field. The recommendations of faculty members deem whether the work is published. Any required revisions are returned to the author to make changes. A final version of the manuscript is then prepared to publish in the journal.

ACKNOWLEDGEMENTS

We would like to thank our faculty reviewers for giving their time to review student submissions. We would also like to thank Dr. DuVinage and the Maryland Center for Undergraduate Research and Dr. Kaci Thompson and the Howard Hughes Medical Institute for providing support, guidance, and funding.

HHMI

MCUR MARYLAND CENTER FOR UNDERGRADUATE RESEARCH

NEWS & FEATURES

HOW TO BE A SUCESSFUL BUSINESS MANAGER:

Interview with Dr. Karen Wouters

BY ROSIE ZHANG

While not many may know of the various research opportunities available in the field of business, Dr. Karen Wouters, a lecturer and director of the MBA Consulting program at the Robert H. Smith School of Business at the University of Maryland, is striving to discover some of the secrets behind management that differentiates successful versus failing companies. Management is just one of the topics studied by research associates, professors, and students at the Smith School, ranked 7th in the world for business research by a study from the University of Texas.

Wouters was born and raised in Belgium, where she received her Ph.D. in Applied Economic Sciences and M.S. in Human Resource development. Wouters first entered the world of business research during her Ph.D, where she played a pivotal role as a researcher for the Flemish government. Wouters enjoys conducting applied research the most because companies can directly apply her results to their own management practices. Wouters attributes much of her success to "the fun in working with others" and successfully collaborating with companies.

Lecturer Dr. Karen Wouters.

Presently, Wouters, also an executive coach as part of the Smith School's eMBA program, is working to develop a model to help coach MBA and undergraduate business students. Wouters applauds the Smith School for the "exceptional model for research" that the eMBA program conveniently provides. Wouters address the questions of what makes a coach a good coach and what makes a client a good client in her current research. She is studying the various techniques that can be used to train managers and clients. Furthermore, Wouters is performing research on the role of E-learning in management training and working to conduct experiments at the county level by collaborating with a software company that develops E-learning programs for polling training. Wouters hopes that her research will help to find the key in allowing for the coaching process to be more streamlined, and thus produce more top-of-the-line executive managers. Unfortunately according to Wouters, "research is typically one step behind business."

Of course, with every research endeavor comes many challenges. Wouter described how difficult it was to control outside factors in business research. "Oftentimes research must be conducted while executives are on the job, "she says. In addition, much of business research is very longitudinal, meaning several years may pass before any significant results can be extrapolated.

For Wouters, a highlight of her research came in the form of a request for a presentation at the Smith School by the Norwegian Embassy. According to Wouters, "They loved it and it made us even more motivated to continue to work." Wouters adds that research can be quite fun, especially if there is the opportunity to work with others on the project. Wouters says she also enjoys "attending conferences because it is interesting to share research experiences with [others]."

Although Wouters did not have the opportunity to start researching until after her undergraduate years, she suggests students begin as early as possible. According to Wouters, "it is oftentimes hard to learn as much on-the-job material while sitting in class." Undergraduate students can volunteer over the semester or over the summer to help professors and research associates at the business school with research. If you are interested in working with Dr. Wouters, you may contact her at kwouter1@umd.edu.

DIGGING for an answer...

By: Niklas Berry

Anthropology Professor Mark Leone shares details regarding his ongoing dig at Wye House in Talbot County

For the past 30 years, University of Maryland Anthropology Professor Mark Leone has directed Archaeology in Annapolis, a research project excavating a wide range of historical sites throughout the capital city. Leone is currently excavating Wye House Plantation in Talbot County, and has made some revealing discoveries.

Wye House has a very remarkable history. Built in the late 18th century by the Lloyd family, it was home to hundreds of slaves including Frederick Douglass. Leone and his research team were approached by the current residents of Wye House as well as the descendants of free blacks who reside in nearby Unionville. Leone says he listened to both groups share what they already knew about the site and what they wanted to know.

Wye House Orangery.

They primarily sought to learn what was left of the slaves' heritage from Africa, as well as their spirituality or religion. Leone and his team excavated the orangery, where slaves lived and grew food. Buried under the floor of the orangery, they found a bundle: a clay bag/pouch containing items like lead shot (small balls of lead), pins, nails, and a small stone axe. Bundles are ubiquitous across Western and Central Africa, so finding one on the Eastern Shore provides physical evidence of a connection between the slaves and their African roots.

Leone said the bundle found in the orangery has the same meaning as one found in Africa, but this one was adopted for American use. "Bundles were designed to manage or control a spirit of the dead for human purposes," Leone said. Although the slaves on the Wye House Plantation were Christian, the bundles served as an everyday expression of how people dealt with protection and well-being, indicating that they used African spiritual objects in their day-to-day life.

In the orangery, Leone also excavated fossilized pollen and analyzed it, which revealed that the slaves cultivated many greens and experimented with many different types of plants.

Leone's findings have excited many people; his work at Wye House and his excavation of the bundle has been featured in numerous media outlets. Because the discovery is a clear connection between 2nd and 3rd generation slaves and their spiritual African heritage, it is a very important and fascinating discovery, especially for the African-American community.

Leone runs a field school during the summer in Annapolis and at the Wye House site for undergraduate students interested in archaeology. The six-week course is a great way for those who are interested in archaeology to get field experience and work in all aspects of an excavation.

HHMI Symposium

By: Jenny Wang

From tuberculosis to leishmaniasis, the 12th annual Howard Hughes Medical Institute (HHMI) Research Symposium on March 3 boasted nearly 30 undergraduate research projects. Undergraduate researchers exhibited colorful posters in the Colonnade of the Bioscience Research Building, enthusiastically presenting about subjects as varied as cadaveric legs to oyster shells. The HHMI grant helps fund undergraduate students conducting independent research projects under the mentorship of faculty members. Students receive stipends to do their research, funds for research supplies, and the opportunity to present their results at professional conferences across the country. Each year, HHMI fellows present the fruits of their research via a poster presentation. Faculty members, campus dignitaries, and aspiring researchers wind around presenters, pausing occasionally to inquire about the research and the research process. "Students from the freshman seminar class called Catalyst are finding out about the breadth of opportunities available on campus and getting to talk to students who are actually doing undergraduate research," said Dr. Kaci Thompson, associate director of the HHMI Program. "[These presenters] are role models for [freshmen]." Both Thompson and HHMI fellows were happy to dole out advice to freshmen looking to get into research.

#1: Find a Lab

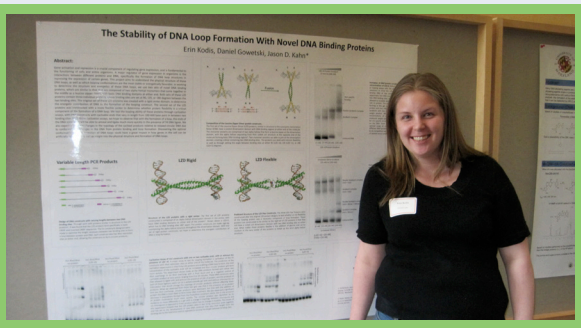
There are lots of opportunities, both on and off-campus, but students have to take initiative and go looking for them. Thompson offered the HHMI office as a good starting point.

"My office has a lot of resources that can help students," she said. "There's a lot available on the web; there's a lot on the CMNS undergrad news and other campus newsletters that fill students in on programs and financial opportunities."

Finding a lab can be the most difficult part of the process. Most inquiries end in rejection, but the key is persistence. "I probably contacted dozens and dozens of people, and I only heard back from [neurophysiology professor] Dr. [Daphne] Soares and one other place," said Adina Schwartz, a junior physiology and neurobiology major researching cavefish in Soares's Neuroethology Lab. "Space is limited, but definitely keep persevering because there will definitely be an option if you keep trying."

#2: Design a Project

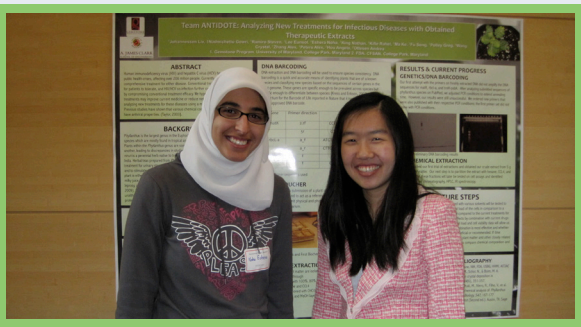
Most HHMI researchers, like Schwartz, were given projects by their faculty supervisors. Others created their own research questions and then sought out labs interested in pursuing the project. Junior general biology major Crystal Wang, a member of Gemstone Team Antidote, was inspired first on a study abroad trip to Peru and then at an NIH lab. In Peru, she learned about a plant active against HIV; at the NIH, she learned about HIV/HCV co-infection. "I decided to see what would happen if we tested this chemical extract of this little-known plant on actual cell culture systems. I found the right people to make it work and now we're doing it," Wang said.



Erin Kodis, senior cell biology/molecular genetics major
The stability and energetics of DNA loop formation

#3: Apply for HHMI Funding

The HHMI grant is an attractive incentive to get into research. The awarding of funds is very selective. Thompson's advice for a competitive application is a strong, thorough proposal. "If the proposal is really strong, they're probably going to get funded," Thompson said. "If their proposal is weak, no matter how good their grades are, no matter how good the kernel of their idea is, the proposal is what carries the application." Current HHMI fellows admitted that the application process was difficult but rewarding. By writing the proposal, they were able to bolster their understanding of their research. Erin Kodis, who is researching protein-DNA energetics in Biochemistry Associate Professor Jason Kahn's lab, found that writing the proposal focused her research. "I wrote the proposal really early on in joining the lab and that was sort of the 'this is what I'm doing, this is why I'm doing it' moment," said Kodis.



Crystal Wang, junior general biology major & Noha Eshera, junior physiology/neurobiology major
Gemstone Team Antidote
Comparison of Phyllanthus niruri plant extract to conventional treatment of HIV/HCV co-infection

#4: Put in Time

Research and hands-on experimentation require a large time commitment. The members of Team Antidote scheduled intense bouts of data collection over winter and summer breaks at the NIH for their cell culture studies. As full-time students working during the school year, undergraduates have to expertly balance their time between classes and research. "I put in about 20 hours a week," said Kodis. "It's time management, but for a lot of days, you think, 'Oh, I have to wait for my gel for two hours, I can do homework in this time.'"

Adina Schwartz, junior physiology/neurobiology major
Comparative startle responses of Astyanax mexicanus

#5: Rock and Roll

Kodis does not regret the large portion of the week that she dedicates to lab work. "It's something I really enjoy," she said. Research requires great effort: to get into the lab, to obtain funding, and to work during the school semester. However, throughout the symposium, the HHMI fellows were all smiles about their final products. Some fellows, like Kodis, plan to continue research in graduate programs, and others hope to incorporate research into their careers. Schwartz is applying to medical school, but she is now reconsidering her options. "I don't want to give up research," said Schwartz. "I really love it."

Searching for Solution X

By: Maia Werbos

For some, it was just another weekday afternoon. For the middle-school girls and mentors in the Girls Excelling in Math and Science (GEMS) program, it was time to solve a mystery.

"A student's science fair project – Solution X, The Cure for the Common Cold – was stolen from a nearby school recently," explained Megan Sanquist, a mentor for GEMS, to the class. "We have six suspects." Another mentor read off the names of the suspects: "Kat Chacold. Ivana Tishu. Ronnie Nose..."

The girls laughed, but there was serious work afoot. Their mission? Analyze the thief's ransom note to figure out which of the suspects had a pen that could have written the note. Today, they were using a technique called chromatography. Chromatography generally refers to a class of forensic techniques, but for them, its meaning was very literal: they were studying the colors that were produced when the inks were separated out in water. They drew a line across the paper with the pen they were testing, dipped it in water, and watched the colors slowly crawl up the white slips.

"Oooh, that one's pretty!" one girl exclaimed.

Lessons like this may seem trivial, but to the GEMS program, they fulfill a vital mission: teaching students to think like scientists. They learn to form hypotheses, design experiments to test their hypotheses, and compare their results to what they expected. In the chromatography experiment, they also discussed the validity of their results: Could someone be convicted based only on the color of their pen? Of course not. "DNA evidence would be better," one student suggested.

GEMS began in 2006 when Edna Crocker and Joelle Carter, backed by the American Association of University Women (AAUW) and the University of Maryland's College of Computer, Mathematical and Physical Sciences' STAND program (Science and Technology Addressing the Need for Diversity), had the idea to create a program that would inspire girls to go into math and science by teaching them to think critically and enjoy the scientific process. The mentoring aspect of the program would be very important as well; having female role models in science would help the girls to identify with math and science, and not feel intimidated by a male-dominated field. GEMS started as a pilot program at Hyattsville Middle School, and has since grown to encompass Nicholas Orem Middle School and William Wirt Middle School, all in Prince George's County.

About a dozen UMD mentors volunteer for GEMS each week. STAND has now dissolved, but GEMS continues to recruit students and collaborate with various campus groups, including the Women in Mathematics group, Women in Engineering, AstroTerps, Women in Physics, and the Alpha Omega Epsilon engineering sorority, which held a 5K run to raise money for GEMS last year.

GEMS lesson plans are focused on hands-on exercises to help students learn actively. Research in educational psychology, established by researchers like K. Ericsson as early

Beautiful ink smears resulted from the chromatography activity. Students compared them to smears from a 'ransom note' and analyzed their results.

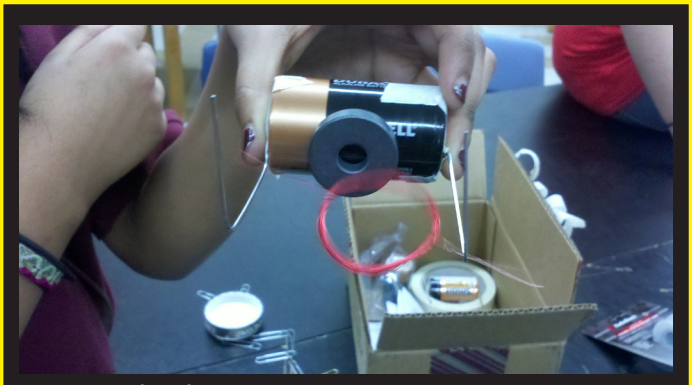
as 1993, shows that a process called deliberate practice may be the best way to gain expertise: that is, people learn a skill best by taking on a challenge appropriate for their level. GEMS mentors and directors strive to challenge students and to make the material accessible and interesting by providing examples of physical principles, and by proving their assertions with real data that the students can see. For example, to teach students about electricity, GEMS used a lesson that gave the students an opportunity to play with light bulbs in series and in parallel circuits, and encouraged them to test the mathematical principles behind circuits themselves. GEMS uses educational research to build a new generation of researchers, also using its own mentor and student surveys to test the effectiveness of different strategies.

But, as the director Edna Crocker says, GEMS is not a tutoring program, "it's enrichment." GEMS is about "stimulating girls' interest" in math and science. According to Crocker, the middle-school age group is a critical age when students can lose interest in math and science, or get really excited about continuing their studies. Mentor involvement is also very important, Crocker says, because mentors discussing their own experiences makes students more interested in college. So GEMS' real mission is to help students enjoy math and science, independent of classes, homework, and exams.

Perhaps the most important thing mentors do in GEMS is encourage students to form their own hypotheses and experiments. Students often ask questions and make suggestions on their own, like "What happens if we change the procedure for dipping the paper and ink in water?", "What happens if we try to use hand sanitizer to extract DNA instead of alcohol?", and "Why did we get lower voltage this time? Maybe we should test with a different set of electrodes to see if the used-up electrodes were causing the problem."

With the exposure they gain to math and science in GEMS, these girls may very well make the next great discovery in science.

Students left slips of paper slightly immersed in water to allow water to travel up the paper by capillary action.



At another GEMS session, students built small electric motors out of a D-cell battery, magnet, and loops of enamel-coated-wire. The loops of wire are whirling furiously!

APPLIED SCIENCES

MOBILE PHONES AS A MEDICAL DIAGNOSTIC PLATFORM WITH A FOCUS ON LOW-POWER AM MODULATION

ANDREW J. DUPREE, JEREMY RAHE, & ERIC BREWER

ABSTRACT

In the developing world, many people die every day due to lack of access to basic medical measurements such as blood pressure and corresponding diagnoses. In order to combat this, a medical diagnostic platform is being designed which will use low-cost sensors and utilize the proliferation of mobile phones in emerging regions for computational power. A chief design difficulty in this project has been the implementation of amplitude modulation (necessary to transmit DC information to the mobile phone) on the 3.2V provided by the phone battery. An analysis of the standard modulation IC, ON Semiconductor's MC1496 balanced modulator, is presented, along with modifications and design decisions that demonstrate optimized operation for low-power, DC input, and minimal harmonics.

INTRODUCTION

The proliferation of technology over the last few decades has completely changed the world we live in. New high-tech tools have revolutionized fields such as communication, education, business, and health care, among many others. Though no one would argue that computers or the mobile phone have solved all of the world's problems, few would dispute that such tools have affected our lives in exciting and generally positive ways.

Unfortunately, the majority of the world has had very limited, if any, access to these new technologies, which are primarily designed with the wealth and resources of developed countries in mind. The situation is aggravated by the fact that these emerging regions, often lacking quality education, health care, and more, could benefit the most from the prosperity that technology can bring.

The mission of the Technology and Infrastructure for Emerging Regions (TIER) laboratory is to research, develop, and deploy technology solutions for the many challenges of the developing world. This task is not as simple as sending technology from developed countries to places that could benefit from technological

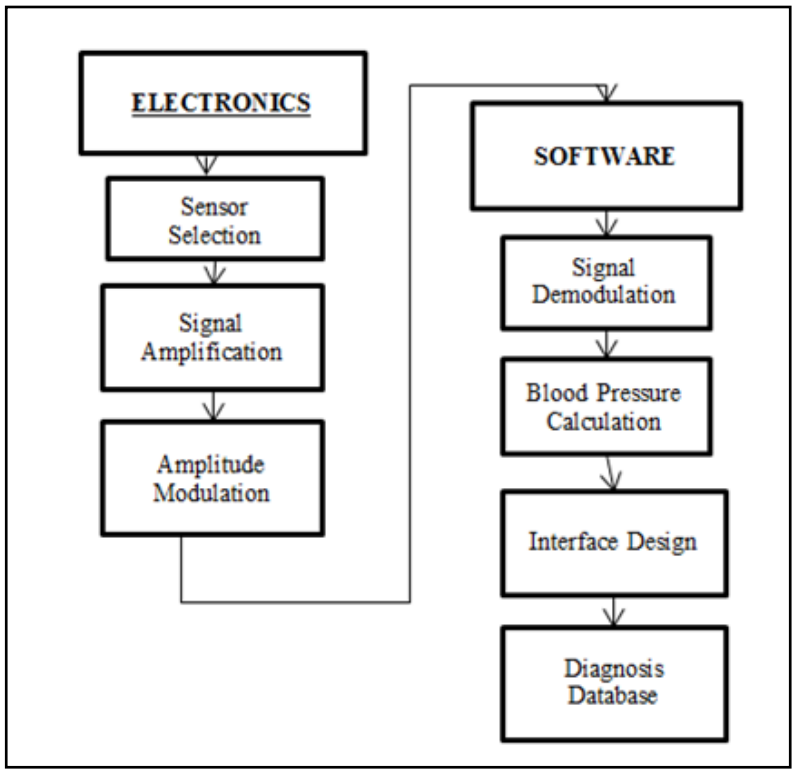


FIGURE 1: A flowchart of the major phases of the Mobile Phone Medical Diagnostic Platform project.

solutions. Effective technology must be designed with the limitations and necessities of its target environment in mind and, if possible, complement the existing infrastructure. One rapidly expanding technological infrastructure in the developing world is the mobile phone network. In 2009, Reuters reported not only that two-thirds of the world's mobile phone subscriptions are in the developing world but also that their presence is helping to stimulate incipient economies.[1] As the mobile phone continues to experience organic growth in emerging regions, the potential applications of this network of computing devices increase as well. As such, TIER has begun a project dedicated to exploring the potential of the mobile phone as a platform for performing useful computations in the developing world.

Some of the most pressing issues facing emerging regions are medical. The "modern medicine" that saves so many lives in the developed world is most often absent in the developing one. Lack of access to basic medical measurements and diagnoses contributes to the death of many people every day. For example, 63,000 pregnant women in developing countries die every year due to a condition called pre-eclampsia. Pre-eclampsia is easily detected by testing for high blood pressure (hypertension), however, this simple procedure is often unavailable.[2] As such, the first application of the mobile phone computational platform that is being investigated is a medical diagnostic platform. By combining mobile phones with low-cost sensors, it is believed that a ubiquitous tool for obtaining vital signs and analyzing their significance can be created. In particular, a tool that reads blood pressure is being developed due to the importance of blood pressure in maternal care.

SCOPE

Broadly speaking, this project can be divided into an electronics phase and a software phase (see Figure 1). The electronics phase involves selecting a suitable pressure sensor, amplifying its output, and modulating the signal for transmission to the phone. The software phase involves demodulating the signal, calculating the blood pressure, creating a GUI for the phone targeted for the regions in which it will be deployed, and creating a database with basic diagnostic information correlated to the blood pressure calculated.

The most pressing challenges for this project lie in the electronics component. A primary objective is to power the entire platform with a standard mobile phone battery, which has a voltage output between 3.2V and 4V. Whether or not it is possible to carry out such tasks as amplitude modulation on 3.2V is a critical question that affects the feasibility of the entire mobile phone medical diagnostic platform.

As such, the majority of the work done thus far, and that which will be discussed in this paper, has been to address this question.

DESIGN

The development platform for our medical devices has been the Nokia N900. Due to its cost, it is not a phone that we would envision targeting our hardware for in the future. However, its ability to run Linux and allow us easy access to the data jacks makes it an ideal platform for our proof-of-concept.

So far, the simplest and most cost-effective way to transmit data from hardware to the phone has been through the microphone jack. Alternative inputs, such as Bluetooth technology, were considered. However, they were rejected due to the additional complexity, power consumption, and cost they would introduce to the design. However, using the microphone jack is not without its challenges. The major obstacle is that a high-pass filter exists on the microphone jack of the Nokia N900, prohibiting DC sensor output from being input to the phone. Though the phenomenon has not been studied carefully, it is believed that this filter serves to eliminate 60 Hz noise that exists in most microphone jacks. To overcome this, we employ amplitude modulation using the standard modulation IC, ON Semiconductor's MC1496.

The MC1496 is a flexible chip, with most biasing and other adjustments external. This makes it ideal for our purposes, considering it will be operated under non-standard conditions. In our custom configuration of the MC1496, there are four primary characteristics for which we design:

1. Low-Voltage
2. DC Input
3. Carrier Suppression
4. Minimal Harmonics

LOW-VOLTAGE

The typical configuration of the MC1496 chip involves dual rails of +12V and -8V. From the battery of the mobile phone, we have but a 3.2V rail with which to work. To solve this, we first employ the single-rail variation

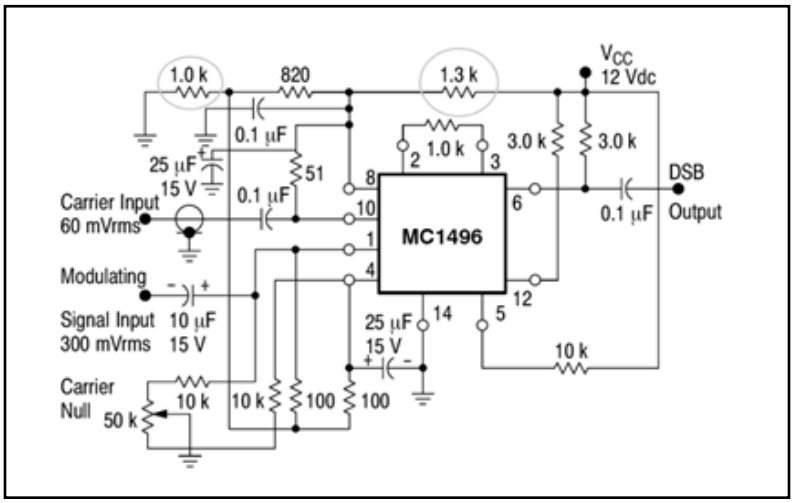


FIGURE 2: The MC1496 Single-Rail circuit from the datasheet.

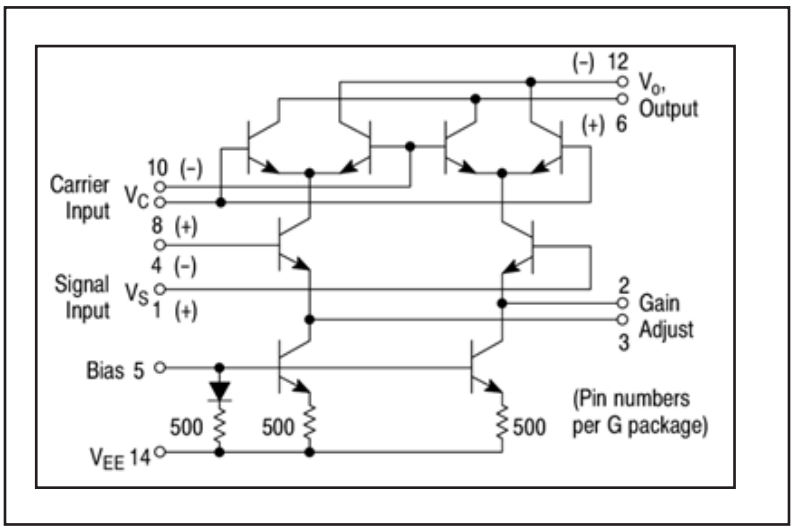


FIGURE 3: Transistor level circuit schematic of the MC1496.

circuit included in the MC1496 data sheet.

This configuration eliminates the negative rail, but still recommends a 12V source. Operation on non-standard voltages requires understanding the transistor level operation of the MC1496.

The modulator is composed of three layers of BJT transistors. The voltage drop across a BJT is around 0.7V. As a consequence, it seems feasible that this circuit could be powered by a 3.2V source with headroom and legroom for an AC output.

The MC1496 datasheet lists the biasing conditions for the circuit as follows:

$$(V_6, V_{12}) - (V_8, V_{10}) \geq 2V$$
$$(V_8, V_{10}) - (V_1, V_4) \geq 2.7V$$
$$(V_1, V_4) - (V_5) \geq 2.7V$$

With relationships such as these, the circuit will ostensibly not run at less than about 6.5V. However, after careful study of BJT biasing conditions and the setup of the MC1496 circuit, one can see that these equations are simplifications of actual BJT biasing restrictions.

The first equation sets the collectors of the output transistors considerably higher than their bases. This is to ensure that the AC output signal oscillating on pins 6 and 12 does not drop the collector voltage below that of the base. The resulting operational mode change (from linear to saturation) could be undesired.

The second equation ensures that the emitter voltage of the carrier-input (top-level) transistors remains well above the base of the modulating signal input (mid-level) transistors. This keeps the mid-level transistors in linear operation.

The third equation keeps the voltage at the base of the mid-level transistors comfortably above the voltage at the collector of the current-source (bottom) transistors. This maintains these transistors in linear operation. With this in mind, one can redefine the biasing equations to more accurately reflect what is physically occurring in the circuit.

$$(V_6, V_{12}) + AV_{in} > (V_8, V_{10})$$
$$(V_8, V_{10}) - 0.7 > (V_1, V_4)$$
$$(V_1, V_4) + AV_{in} > 0.7V$$

With these equations used as guidance, the use of a much lower voltage rail is evident. One must simply monitor the gain of the circuit to maintain correct biasing.

These mathematical results were verified in simulation using National Instruments Multisim. However, before discussing these results, it is first useful to understand the other design choices involved in modulation.

DC INPUT

The single rail MC1496 circuit is AC coupled due to the DC biasing voltage on pin 1. Modifying the circuit for use with a DC input requires a method of adding the sensor output to the bias voltage. To do this, an LM324 Quad Op-Amp is employed. The bias voltage is diverted from pin 1, buffered, and then added to the sensor output using a non-inverting summing amplifier. This final output is then input to pin 1.

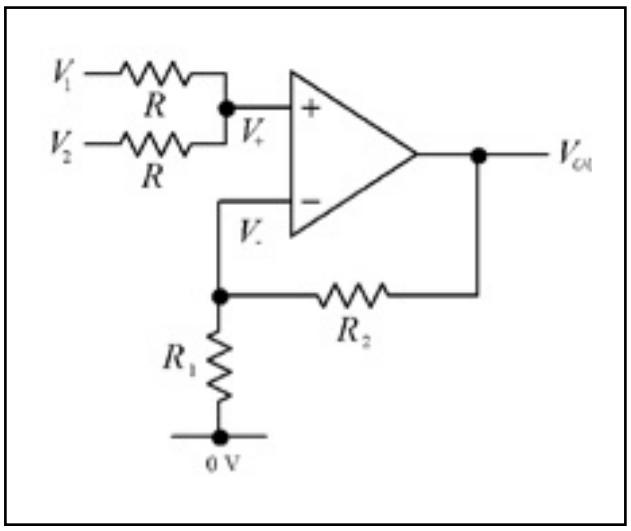


FIGURE 4: A non-inverting summing amplifier.

CARRIER SUPRESSION

An important variable to take into consideration when working with the MC1496 is carrier suppression versus injection. This determines how much of the carrier wave is present in the output signal. In the frequency domain, the carrier wave component is present at the carrier wave frequency. While under ordinary circumstances of AM modulation this would not be a problem as long as proper filtering were employed, any carrier injection would create an unwanted offset when working with DC or low-frequency signals. As such, maximum carrier suppression must be implemented.

The main control of carrier-wave suppression vs. injection in the MC1496 circuit is the carrier null potentiometer (see Figure 2). Balancing the potentiometer reduces gain but suppresses the carrier. Because carrier suppression is most important, the potentiometer is balanced.

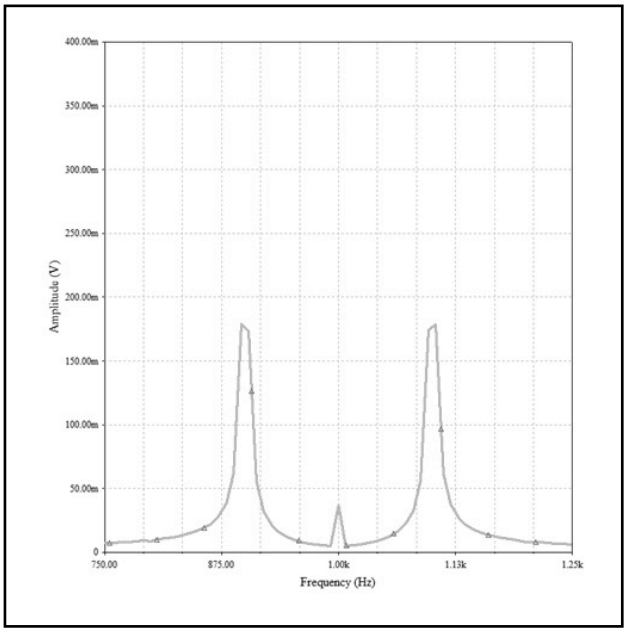


FIGURE 5: Modulator output when carrier null potentiometer is unbalanced.

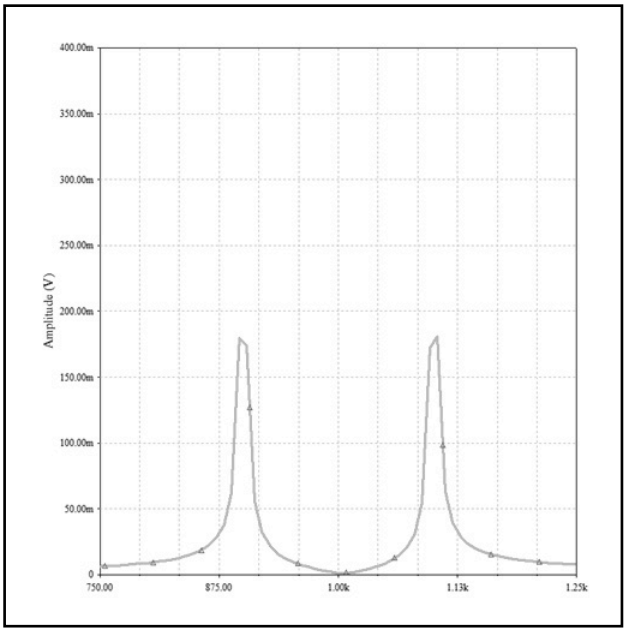


FIGURE 6: Modulator output when the carrier null potentiometer is balanced.

MINIMAL HARMONICS

A final characteristic of the MC1496 modulation circuit that must be carefully controlled is the existence of harmonics in the spectrum of the output. These harmonics – portions of the signal which appear at multiples of the carrier frequency – do not actually harm the part of the spectrum necessary to recover the modulating signal. However, in the future of the project, we plan to add the output from multiple sensors to a single signal by modulating the outputs to different frequencies and then summing them. Harmonics in the output of the modulation would muddle the spectrum of the summed signal and make recovery of the original signals impossible. The mode of operation of the top-level transistors control the harmonic output of the modulator. If the transistors are run in saturation (with a carrier signal input of greater than about 15 mV) gain is increased but harmonics are outputted. A small carrier signal causes the transistors to run in linear mode, resulting in a much smaller gain but a cleaner signal.

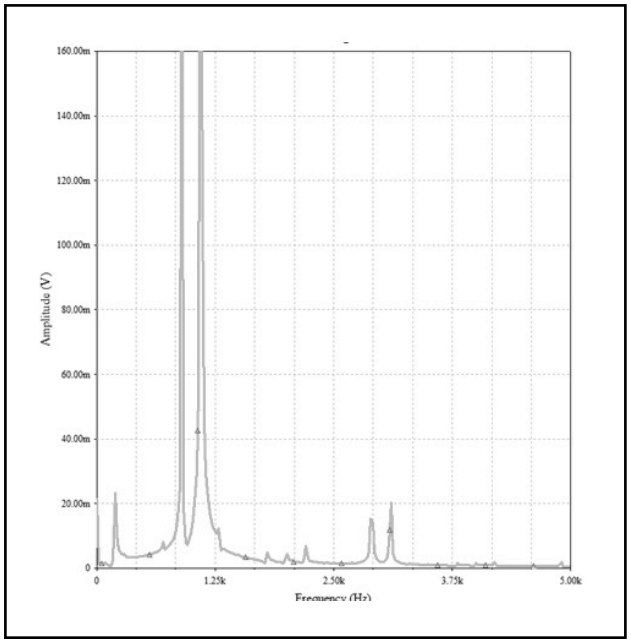


FIGURE 7: Modulator output when the carrier-input transistors are run in saturation.

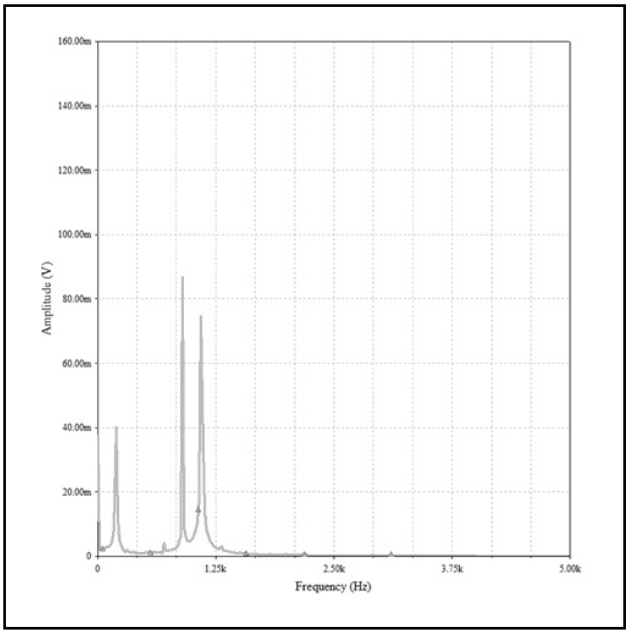


FIGURE 8: Modulator output when the carrier-input transistors are run linearly.

RESULTS

In order to test all of these design choices together, a simulation was performed with a 3.2V source and configured for carrier suppression and minimal harmonics. The results are as follows:

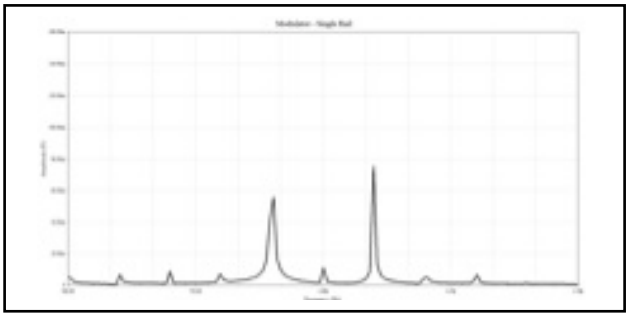


FIGURE 9: The frequency domain of the initial output. Note the carrier injection and harmonics.

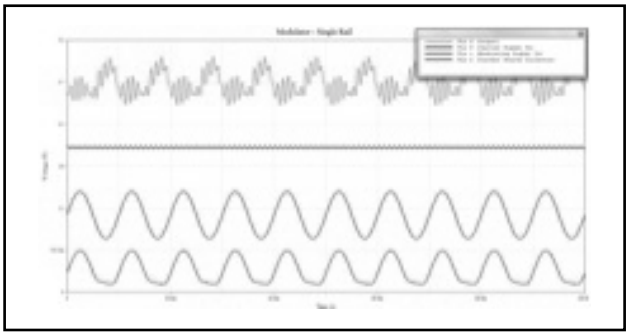


FIGURE 10: The time domain of the initial output. Note the distortion on pin 2.

Note: These simulations were performed with an AC input so as to be able to characterize the carrier suppression. The carrier signal was a 1kHz 15mV sine wave, the modulating signal was a 100 Hz 300mV sine wave.

The initial results of the simulation are not promising. The frequency domain is clearly not ideal, with significant carrier injection and harmonics. Upon inspection of the time domain signal, one can see distortion on the collector of the current source (bottom, pin 2). The signal is "running into" ground. An even closer look reveals that base of the modulating signal input (third from top, pin 1) is dropping below 0.7V, violating one of the guidelines and causing the current source to distort.

This can be remedied by raising the bias voltage on pin 1 slightly. However, it should be noted that this can cause the carrier signal input voltage (second from top, pin 8) to "bump into" the output (top, pin 6). Both of these problems can be dealt with by changing the values of the resistors circled in Figure 2. Increasing the value of the 1k resistor (to around 2k) increases the bias voltage on pin 1, and increasing the value of the 1.3k resistor (to around 2k) drops the voltage on pin 8 to compensate. The resulting signals are much cleaner:

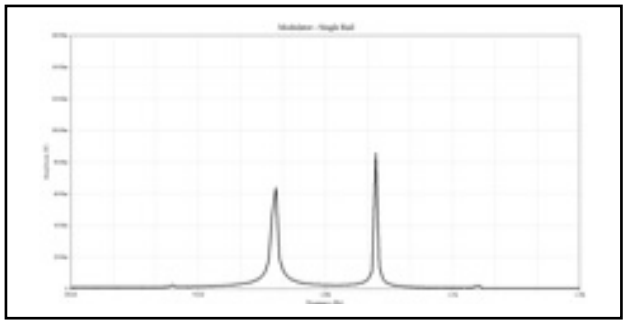


FIGURE 11: The frequency domain of the modified low-power modulator. Note the carrier suppression and lack of harmonics.

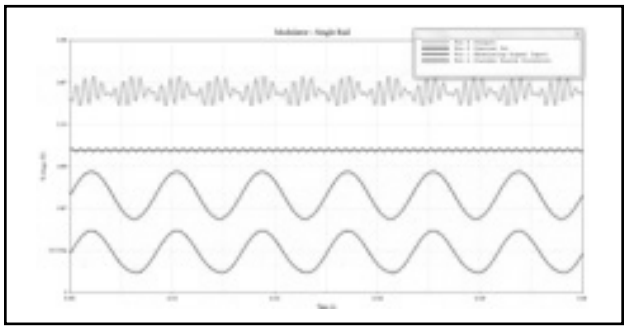


FIGURE 12: The time domain of the modified low-power modulator. Note the lack of distortion.

CARRIER SUPRESSION

The mobile phone battery presents one more challenge in the use of the MC1496 modulator. Depending on the charge of the battery, the voltage output fluctuates between 3.2V and 4V. The MC1496 gain fluctuates with the resulting variable rail. Without some way to determine the gain, precise recovery of the original signal would be impossible.

Once the electronics are integrated with the phone software, we plan to design a calibration system to account for this. Most gauge pressure sensors produce some output even when no pressure is applied. By reading the level of this zero-state output, it should be possible to determine the gain of the circuit for the upcoming measurement.

CONCLUSION

Significant progress has been made on the low-level electronic challenges which threaten the feasibility of this initiative. It has been demonstrated that amplitude modulation using the MC1496 modulator chip can be performed on 3.2V with negligible carrier injection and harmonics. Additionally,

a design has been proposed which allows for the input of a DC signal into the initially AC-coupled circuit. Simulation data has so far been quite positive. These designs will soon be verified in a physically constructed circuit. Following this, work on the other components of the mobile phone based medical diagnostic platform can begin.

ACKNOWLEDGEMENTS

I would like to thank the University of California at Berkeley superb program coordinators for admitting me to the program and providing me with the opportunity to learn so much and grow as an engineer. I must also extend my sincerest gratitude to my faculty advisor Dr. Eric Brewer and my graduate mentor Jeremy Rahe for taking time out of their own busy schedules to start me on this engaging project. A special thanks goes out to the helpful support staff on the National Instruments Multisim forums for assisting with the simulation setup. Finally, I thank the National Science Foundation and the United States Department of Defense for the funding which made this possible.

REFERENCES

1. L. MacInnis. 2009. Mobile phone growth helps poorer states. U.N. Reuters.

2. B. Little. 2010. E-learning helps women survive Eclampsia. eLearn Magazine.

LIFE SCIENCES

ROLES OF STAT 5 AND PI3K IN IL-7 RECEPTOR SIGNAL TRANSDUCTION PATHWAYS

JULIA M. TRITAPOE, TIZIANA CAVINATO, JULIE A HIXON, QIONG JIANG, WEN QING LI. & SCOTT K. DURUM

ABSTRACT

Signals emanating from the IL-7 receptor (IL-7R) play a critical role in lymphocyte development and are required for peripheral T cell homeostasis. The tyrosine 449 residue (Y449) of the intracellular domain of the IL-7α chain (IL-7Rα) has previously been shown to be a region essential to the initiation of IL-7 stimulated signal transduction pathways. This study demonstrates that the Y449 residue is phosphorylated upon IL-7 stimulation. It has been hypothesized that signaling pathways including STAT 5 (signal transducer and activator of transcription) and PI3K (phosphatidylinositol 3-kinases) are activated upon docking to the YVTM (tyrosine, valine, threonine, methionine) motif of the IL-7Rα containing phosphorylated Y449. Specific mutations in regions surrounding Y449 of the IL-7Rα were introduced to determine whether STAT 5 and PI3K pathways directly emanated from the IL-7Rα chain. Disassociating the STAT 5 signal transduction pathway from IL-Rα impaired T cell development in vivo and eliminated the survival response of IL-7 in vitro. Conversely, disassociating the PI3K pathway had no effect on cellular development or survival. The Y449 residue of the IL-7Rα appears to directly couple to and stimulate STAT 5 but not PI3K in the thymic progenitor response to IL-7.

INTRODUCTION

The cytokine interleukin 7 (IL-7) is produced by non-lymphoid cells in lymphoid organs.[1] IL-7 and its associated receptor, IL-7R, play a critical role in lymphocyte development, mainly the protection of cells from apoptotic cell death. IL-7 signaling plays a role in the selective maturation of T cells, and is essential for peripheral T cell homeostasis, incessantly influencing cellular survival and proliferation. In humans, genetic defects in IL-7R are known to cause severe combined immunodeficiency disease (SCID). SCID, also known as the "Bubble Boy Syndrome," is characterized by the absence of T cells and subsequent depleted B cell function. Patients with SCID have severely compromised immune systems and often very short life expectancies, hence IL-7 has promising therapeutic applications. Despite their critical importance, signaling pathways stemming from the IL-7R in response to IL-7 have yet to be fully elucidated.

It has previously been proposed that following IL-7 engagement the IL-7Rα chain cross links with the common γ chain (γc) leading to mutual phosphorylation of tyrosine kinases JAK 1 and JAK 3.[1, 2] Intrinsic enzymatic activity is in-

creased in JAK 1 and JAK 3 upon phosphorylation and they proceed to phosphorylate the Y449 residue in a highly conserved region located near the terminus of the cytoplasmic tail of the IL-7Rα .[2] The JAK-STAT pathway has been shown to be activated by IL-7 in T cells, likewise Y449 has been shown to be essential for B cell signaling and T cell development.[2,3,4] Initial studies linked the PI3K pathway in B cells to the IL-7R by demonstrating direct coupling of p85, the regulatory subunit of PI3K, to the intracellular domain of IL-7Rα. (Figure 1).[5-7]

Although both STAT 5 and PI3K signaling pathways in cultured T cells have been shown to require Y449, the possibility exists that the pathways are not directly coupled to this region of IL-7Rα but rather stimulated downstream of a unique pathway that is coupled directly to Y449. It has previously been revealed that Y449 is critical for STAT 5 binding and phosphorylation, but the precise role of Y449 remains unclear as phosphorylation of Y449, likely an essential requirement for activation of STAT 5 and PI3K pathways, has not yet been demonstrated. Genetic deletions and knock out studies have clarified the role of STAT5 in T cell development. Upon activation, STAT 5 has anti-apoptotic activity and also regulates expression of certain Bcl-2 family members.[1] Furthermore, T cell development is inhibited very early upon deletion of STAT 5 a and b.[8] Although the apparent requirement for STAT 5 in T cell development supports the proposed mechanism of IL-7 signaling, because STAT 5 deletion also impaired IL-7 independent hematopoietic pathways, direct coupling of STAT 5 to IL-7Rα remains questionable. Phosphorylated PI3K regulates the downstream target protein kinase B (AKT). The PI3K- AKT pathway likely supports IL-7 survival signaling by inactivating the pro-apoptotic death protein Bad (Bcl-2 family member).[1]

In this study, we aimed to investigate phosphorylation of the Y449 residue, and to evaluate the possible interaction between phosphorylated Y449 and the STAT 5 and PI3K pathways. The generation of specific mutations in the IL-7Rα allowed selective and independent elimination of the STAT 5 or PI3K signaling pathways, and provided a mechanism to comparatively analyze the relative role that each pathway plays in the development and homeostasis of T cells.

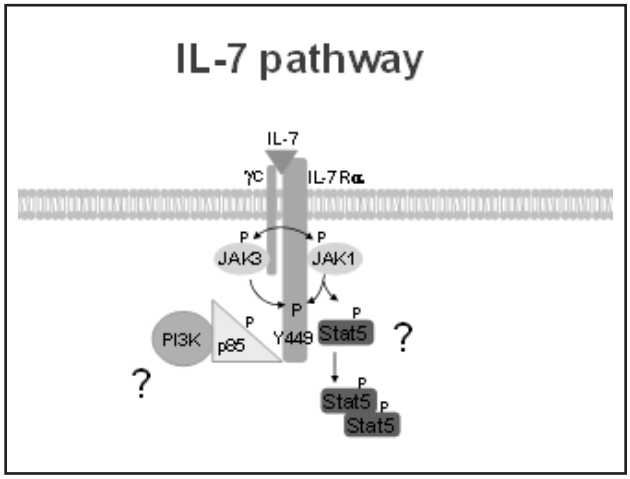


FIGURE 1: Early events in the IL-7 signal transduction pathway. Binding of IL-7 to IL-7Rα induces the recruitment of the γc and subsequent cross linking of the α and common γ chains. Mutual phosphorylation of JAK 3 and JAK 1lead to phosphorylation of the Y449 residue of the IL-7Rα chain. STAT 5 and p85 may be directly coupled and independently activated by phosphorylated Y449.

MATERIALS & METHODS

Cell Lines

The retrovirus packaging cell line

Phoenix-Eco was maintained in Dulbecco's modification of Eagle medium (Mediatech Inc.) and supplemented with 10% FBS (22). The IL-7 dependent mouse thymocyte cell line D1 was maintained in RPMI 1640 (Mediatech Inc.), supplemented with 10% fetal bovine serum (FBS;HyClone), 50μM β-mercaptoethanol (Invirogen), 100U/mL of penicillin, 100μg/mL of streptomycin (Mediatech Inc,) , and 50ng/mL of mouse IL-7 (Pepro Tech).

DNA Constructs

The full length murine IL-7 receptor (mIL-7R) was cloned into the retroviral vector pMIG.2 Mutations were selectively introduced into the mIL-7R via PCR to inhibit STAT 5 and p85 binding. Chimeric receptors containing fused extracellular hIL-4R and transmembrane and intracellular domains of mIL-7R were cloned into the pMIG retroviral vector. All constructs were verified by DNA sequencing.[2]

Retroviral Infection

Constructs were transfected into the Phoenix-Eco packaging cell line using FuGene 6 reagent (Roche). The replication incompetent but infectious retroviral supernatant was collected after 48hr and plated onto a RetroNectin (TaKaRa) coated plate. D1 cells were added and infected overnight, after one week GFP positive cells were sorted. The stable cell lines expressing different chimeric receptors were maintained in mIL-7. Bone marrow cells were cultured for 48hr and infected by plating on RetroNectin coated plates with the different retroviral supernatants. The infection was repeated after 72hr.

MTT assay

At a density of 5 x 104 cells/well, D1 cells were plated in 96-well plates and incubated for 24 and 48 hr. 8μl of MTT was added (5mg/ml; Sigma) and cells were incubated for 4 to 6hr. 100μl of solubilization solution (Promega) was added, and cells were incubated overnight at 37 °C. Plates were read by spectrophotometer at wavelengths of 570 and 620nm.

Phospho-STAT5 intracellular staining

Single cell thymoctye suspensions were prepared from normal C57BL/6 mice. Thymocyte populations were stimulated 20 min with mIL-7, and cells were prepared for intracellular staining of phospho-STAT 5.[11] Permeabilization of the cells was performed in the presence of PE-conjugated anti-phosphor-STAT 5 (Tyr694) (BD Pharmingen). Cells (2 x 106) were incubated for 1 hr in the dark, washed twice in PBS plus 1% FCS, and analyzed on a FACScan.

Immunprecipitation and immunoblotting

Cell lysates were prepared from 1 x 108 D1 cells cultured for 4 hr supplemented with 50ng/mL IL-7 or starved of IL-7. Phospho-stop (Roche) phosphatase inhibitor was added to the cell lysis buffer, calyculin was used to inhibit PTEN. Anti-phosphotyrosine, clone 4G10, was used for immunoprecipitation (Millipore). Protein supernatants were separated by SDS-PAGE and transferred to nitrocellulose. Western blot analysis was performed using anti-phosphotyrosine 449 (Rockland) (1:10,000 dilution in BSA) and anti-phospho Akt (ser473)

(1:1000 dilution in BSA, Cell Signaling). After incubating overnight at 4°C the proteins were visualized using anti-rabbit IgG secondary antibody conjugated to HRP (1:2000 dilution, Cell Signaling) and a chemiluminescence detection system (Amersham).

RESULTS

Evaluation of the role of Y449 in STAT 5 and P13K signaling pathways in vivo

The YXXM motif favored by p85 and the YV/L motif favored by STAT 5 both exist in the YVTM sequence containing Y449 of the IL-7Rα .[5-7] Mutations in these favored motifs were independently introduced to allow elimination of one of the pathways but retention of the other. In order to observe the possible induction of STAT 5 and PI3K pathways in the IL-7 dependent murine thymocyte cell line D1, a chimeric receptor involving fusion of the mutated intracellular membrane region of the mouse IL-7Rα to the extracellular domain region of the human IL-4R was designed.

As detected by intracellular staining for phosphorylated STAT 5, mutation of V to R in the second position of the targeted motif eliminated the stimulatory response of IL-4 in transfected D1 cells (Figure 2). This specific region can hence be rendered as a required site for the activation of STAT 5. As predicted, mutating the site essential for STAT 5 activation significantly decreased survival of D1 cells (Figure 3). Eliminating the site proposed to be required for p85 activation, which involved mutating the fourth position of the targeted motif from M to L, was inconclusive as the PI3K pathway could not be detected in our model. There was little effect on D1 cell survival upon elimination of the site proposed to be required for p85 activation (Figure 3).

The IL-7R and Y449 have previously been shown to be essential in thymic development of T cells.[1,2] To test for the requirement of STAT 5 and PI3K-AKT pathways emanating from Y449, IL-7Rα deficient hematopoietic progenitors were reconstituted with IL-7Rα or its mutants by retroviral infection. As previously shown, mutating the STAT 5 site inhibited thymic T cell development.[1,2] However, eliminating the p85 site had no apparent effect on T cell development. Receptors bearing simultaneous mutations in both p85 and STAT 5 sites showed impairment in T cell development resembling that of the STAT 5 mutation alone. Consequently, it appears that the IL-7Rα signal transduction path

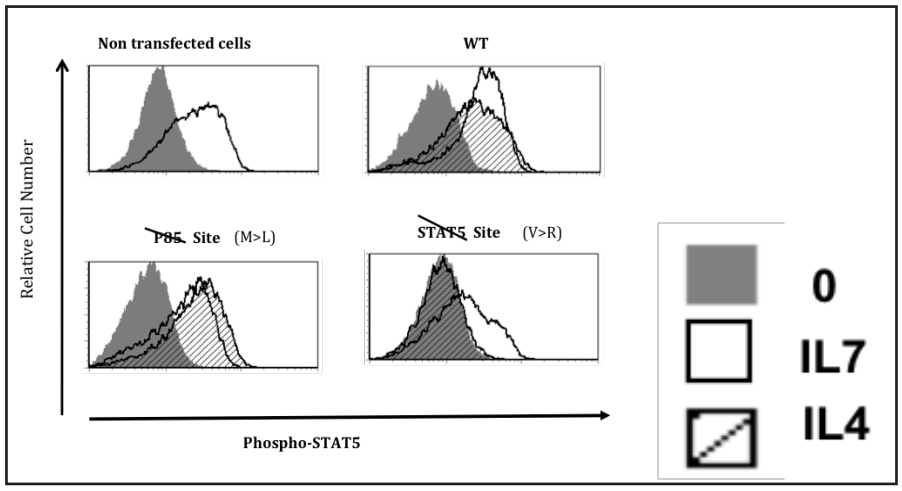


FIGURE 2: Intracellular staining of phospho-STAT 5. D1 cells with the indicatedIL-7 receptors were stimulated for 20min by IL-7 and stained for intracellular phospho-STAT 5.

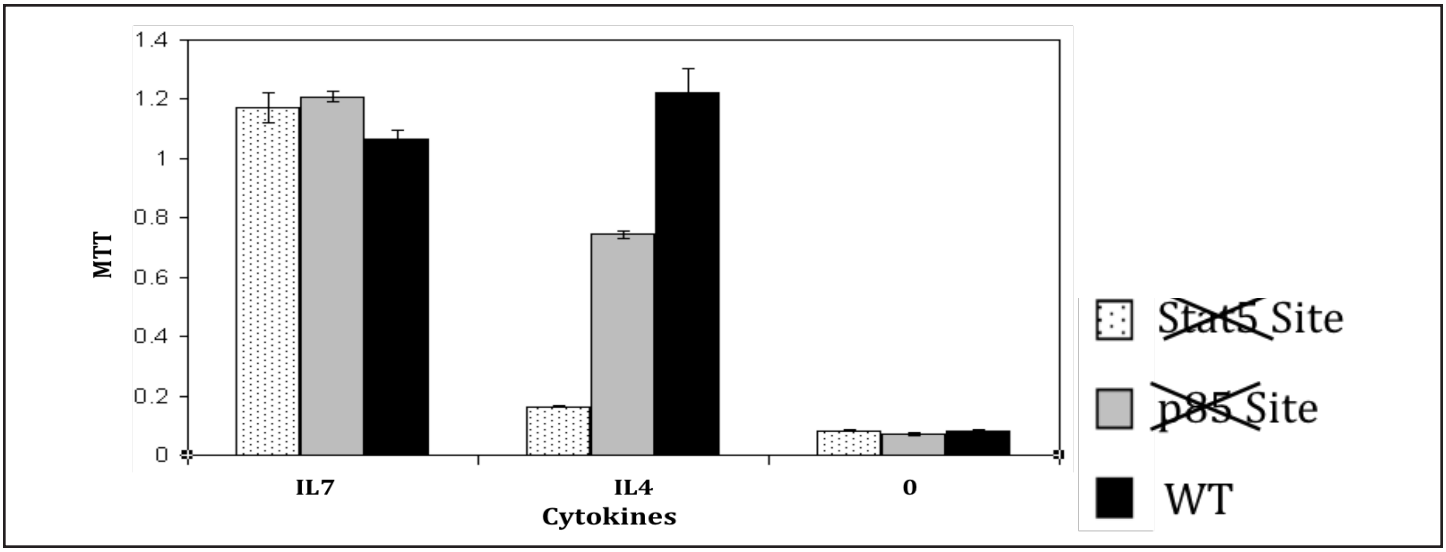


FIGURE 3: Survival effect of uncoupling STAT 5 and PI3K pathways from IL-7R. Chimeric receptors in D1 cells were stimulated by IL-4 to test the effects on survival as a result of uncoupling STAT 5 and PI3K pathways from IL-7R.

way emanating from Y449 requires the STAT 5 pathway, but not the PI3K pathway.

Phosphorylation via IL-7 stimulation

STAT 5 is rapidly phosphorylated during IL-7 stimulation of primary murine spleen cells (Figure 4). A response to IL-7 stimulation was detected within twenty minutes in CD4 and CD8 T cells. After a stimulation period of twenty minutes, a withdrawal of IL-7 lead to a steady decline in STAT 5 phosphorylation. Near complete dephosphorylation of STAT 5 was detected within two hours after withdrawal.

The Y449 residue present in the intracellular domain of the IL-7Rα has been shown to be essential for STAT 5 phosphorylation, and to play a critical role in T cell development.[1,2,8-11] It is theorized that Y449 serves as a docking site for STAT 5, and that upon Y449 phosphorylation, STAT 5 binds to Y449 via its SH2 domain and is subsequently phosphorylated. Despite the observed importance of Y449, phosphorylation of Y449 has not been demonstrated.

To analyze the role of phosphorylated Y449 in IL-7 signal transduction, an anti-peptide antiserum was created to recognize phosphorylated Y449 of the IL-7Rα chain. The designed anti-peptide antiserum was constructed so as not to react with unphosphorylated Y449 (Figure 5A). To determine whether Y449 was indeed phosphorylated via IL-7 stimulation, D1 cells were stimulated by IL-7 for 20 minutes. Cell lysates were prepared and phosphoproteins were isolated via immunprecipitation using antiphosphotyrosine 4G10. Analysis of the phosphoproteins by immunoblot using the generated anti-Y449 peptide antisera and anti-IL-7Rα revealed that Y449 of IL-7R was phosphorylated only in DI cells stimulated by IL-7 (Figure 5B). Our findings fully support the proposed mechanism of initial Y449 phosphorylation, followed by STAT 5 binding and phosphorylation.

Y449 is contained in a peptide with a docking site for p85, thus it has been proposed that the PI3K-AKT pathway could be directly activated via phosphorylation of Y449.[8,12] However, stimulation by IL-7 continuously failed

to yield induced phosphorylation of AKT (protein kinase B) in D1 cells or in primary T cells. AKT phosphorylation does appear to be involved in the proposed model though as constitutive phosphorylation was observed in D1 cells by blocking PIP3 (phosphatidylinositol (3,4,5)-trisphosphate) dephosphorylation by inhibition of PTEN (phosphatase and tensin homolog) with calyculin (Figure 6). Loss of PTEN function coupled with activation of the PI3K pathway results in PIP3 accumulation. PIP3 recruits AKT to the plasma membrane where it is further activated by PDK1 (3-phosphoinositide-dependent protein kinase-1).[13] Although there may be a role of the PI3K-AKT pathway in T cell progenitors, our data supports that IL-7 stimulation does not significantly induce the PI3K-AKT pathway.

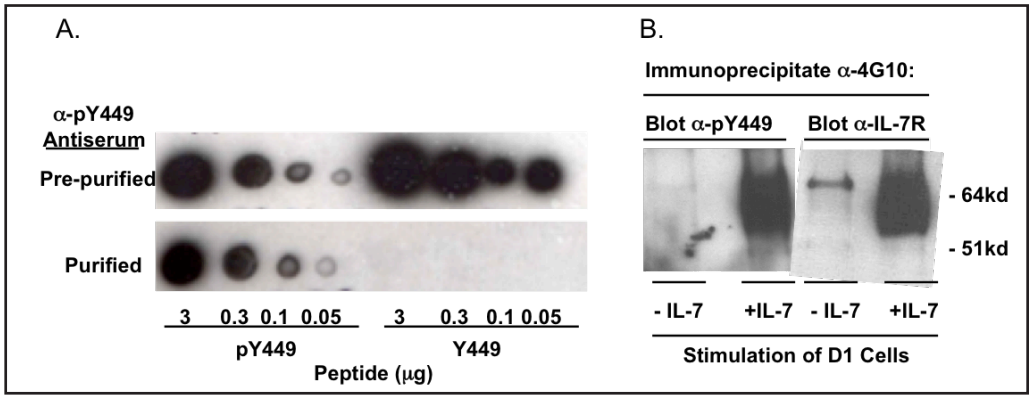


FIGURE 5: Detection of phosphorylated Y449 and IL-7Rα in D1 cells. Panel A shows the reaction of pY449 antiserum with phosphorylated or unphosphorylated peptide (upper), followed by purification to achieve reactivity to phosphorylated Y449 only (lower). In panel B, D1 cells were stimulated with IL-7, cell lysates were immunoprecipitated with anti-phosphotyrosine. Western Blot analysis was performed using anti –IL-7R and anti-pY449, a rabbit antiserum specific for phosphorylated Y449.

DISCUSSION

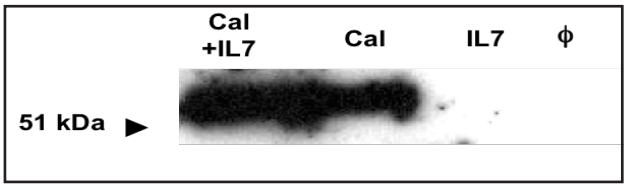


FIGURE 6: Phosphorylation of AKT. D1 cells were stimulated by IL-7 for 20min. Calyculin was selectively added to cell lysate to block dephosphorylation of PIP3 by PTEN.

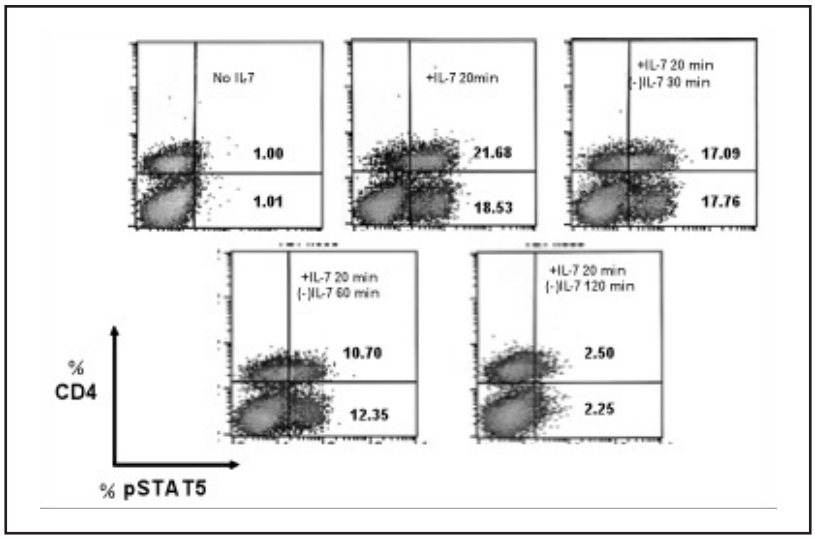


FIGURE 4: STAT 5 phosphorylation in murine spleen cells. Spleen cells were stimulated by IL-7 for 20 minutes and deprived of IL-7 for up to 2 hr. STAT 5 phosphorylation in response to IL-7 stimulation/deprivation was assessed through staining with anti-CD4 and anti-phospho-STAT 5, and subsequent analysis by flow cytometry. Numbers in the quadrants represent relative percentages.

Various components of the IL-7 signal transduction pathway are of great significance to the development, maturation, and prolonged lifecycle of lymphocytes. Thus understanding the complete mechanistic emanation of pathways from IL-7R is of critical importance. Y449 in particular has previously been shown to be an essential site on IL-7Rα. It has been proposed that the YVTM motif containing the Y449 acts as a docking site for key mediators of IL-7 signaling such as STAT 5 and p85.[2,13] It has also been suggested that PI3K and STAT

5 pathways are activated upon coupling to the YVTM motif when Y449 is phosphorylated. By selectively uncoupling the STAT 5 or PI3K pathways from IL-7R via introduced mutations near the Y449 residue, this study revealed a requirement for the STAT 5 but not PI3K pathway in IL-7 signal transduction.

PI3K is influential in many fundamental cellular functions involving metabolism, cell cycle progression, and overall survival.16Although the PI3K pathway does not appear to be directly coupled to IL-7Rα, studies have shown activation downstream of JAK 3 and STAT 5 in T cells, and furthermore defective mutations in STAT 5 inhibited IL- 7 activation of PI3K.[15, 16]

Y449 has been shown to be of critical importance in the IL-7 signal transduction pathway, activating STAT 5 and playing a critical role in T cell development. This study aimed to determine the mechanism through which Y449 acts to influence T cell survival and proliferation. The development of antiserum against phosphorylated Y449 peptide allowed us to show that Y449 is indeed phosphorylated in response to IL-7 stimulation. It is important to note that there was little specific reactivity of the antiserum using whole cell lysate. Poor detection of phosphorylated Y449 could signify its instability or, simply, very low levels of phosphorylation (perhaps only a fraction of the IL-7Rα was being phosphorylated). An alternate explanation could be that anti-phospho Y449 is a very low affinity antibody. In order to improve detection of phosphorylated Y449 and to enrich phosphoproteins present in the cell lysate, immunoprecipitation with anti-phosphotyrosine (4G10) was used prior to western blot analysis.

Inhibiting STAT 5 binding to IL-7Rα indeed blocked T cell development. However accumulation of peripheral T cells was detected in the spleen, thus other unique signaling pathways must contribute to survival and proliferation signals emanating from IL-7R. Other STAT pathways (1 and 3) have shown to be activated independent of Y449 and could be influencing peripheral survival and expansion of T cells.1 Future areas of research include binding studies to examine whether STAT 5 binding is truly abrogated in mutant IL-7 receptors. To detect STAT 5 binding, non chimeric murine IL-7 receptors will be mutated in the favored STAT 5 binding motif and flag tagged. The mutant receptors will be immunoprecipitated, and analyzed by Western blot using an anti-phospho STAT 5 antibody. In the future, we also plan to further investigate the possible role of STAT pathways in the homeostatic function of IL-7, and in the expansion of peripheral T cells in an in vivo mouse model.

REFERENCES

1. Jiang, Q., W.Q. Li, F.B. Aiello, et al. 2005. Cell biology of IL-7, a key lymphotrophin. Cytokine Growth Factor Review. 16(4-5):513-33.

2. Jiang, Q., W.Q. Li, R.R. Hofmeister, et al. 2004. Distinct regions of the interleukin-7 receptor regulate different Bcl2 family members. Molecular and Cellular Biology. 24(14):6501.

3. Foxwell, B.M., Beadling, C., Guschin, D..

et al. 1995. Interleukin-7 can induce the activation of Jak 1, Jak 3 and STAT 5 proteins in murine T cells. European Journal of Immunology. 25(11):3041.

4. Lin, J.X., T.S. Migone, M. Tsang, et al. 1995. The role of shared receptor motifs and common Stat proteins in the generation of cytokine pleiotropy and redundancy by IL-2, IL-4, IL-7, IL-13, and IL-15. Immunity. 2(4):331.

5. Demoulin, J.B., Uyttenhove, C., Van, R.E, et al. 1996. A single tyrosine of the interleukin-9 (IL-9) receptor is required for STAT activation, antiapoptotic activity, and growth regulation by IL-9. Molecular and Cellular Biology. 16(9):4710.

6. Porter, B.O., Scibelli, P., Malek, T.R.. 2001. Control of T cell development in vivo by subdomains within the IL-7 receptor alpha-chain cytoplasmic tail. Journal of Immunology. 166(1):262.

7. Corcoran, A.E., Smart, F.M., Cowling, R.J., et al. 1996. The interleukin-7 receptor alpha chain transmits distinct signals for proliferation and differentiation during B lymphopoiesis. EMBO Journal. 15(8):1924.

8. Yao, Z., Y.Cui, W.T. Watford, et al. 2006. Stat5a/b are essential for normal lymphoid development and differentiation. Proc. Natl. Acad. Sci. U.S.A.. 103:1000

9. Pallard, C., Stegmann, A.P., Smart, F., et al.. 1999. Distinct roles of the phosphatidylinositol 3-kinase and STAT5 pathways in IL-7-mediated development of human thymocyte precursors. Immunity. 10(5):525.

10. Osborne, L.C., Dhanji, S., Snow, J.W., et al. 2007. Impaired CD8 T cell memory and CD4 T cell primary responses in IL-7R alpha mutant mice. The Journal of Experimental Medicine. 204(3):619.

11. Van De Wiele, C.J., Marino, J.H., Murray, B.W., et al. 2004. Thymocytes between the beta-selection and positive selection checkpoints are nonresponsive to IL-7 as assessed by STAT-5 phosphorylation. Journal of Immunology. 172(7):4235.

12. Venkitaraman, A.R., Cowling, R.J. 1994. Interleukin-7 induces the association of phosphatidylinositol 3-kinase with the alpha chain of the interleukin-7 receptor. European. Journal of Immunology. 24(9):2168

13. Carnero, A., Blanco-Aparicio, C., Renner, O., et al. 2008. The PTEN/PI3K/AKT signaling pathway in cancer, therapeutic implications. Current Cancer Drug Targets .8(3):187-198.

14. Johnson, S.E., Shah, N., Bajer, A.A., et al. 2008. IL-7 activates the phosphatidylinositol 3-kinase/AKT pathway in normal human thymocytes but not normal human B cell precursors. Journal of Immunology. 180(12):8109.

15. Wofford, J.A., H.L. Wieman, Jacobs, S.R., et al. 2008. IL-7 promotes Glut1 trafficking and glucose uptake via STAT5-mediated activation of Akt to support T-cell survival. Blood. 111(4):2101.

16. Manning, B.D., Cantley, L.C. 2007. AKT/PKB signaling: navigating downstream. Cell 129(7):1261.

SPRING 2011

www.scientificterrapin.umd.edu