



## DEAN'S MESSAGE: What's On My Mind



What's on my mind this month are the major transitions occurring across the School of Medicine and how necessary change is for the advancement—of our students, our academic units, our educational curriculum and our leadership team.

**Students:** This month we celebrate convocation and graduation for our remarkable medical, graduate and allied-health students in the Class of 2014.



Graduation is a time for reflection, celebration and a preview of what lies ahead. You have been tested, inspired and motivated to reach your full potential, while maintaining an incredible standard of excellence as you balanced the intense desire to achieve your personal and professional goals. This same passion and determination that brought you to the University of Maryland School of Medicine will be the fuel that advances you throughout your life and career. You join your brilliant predecessors and fellow alumni who have led exceptional careers, transforming medicine and science in profound ways throughout the state and the nation through discoveries, clinical care, and education. **I strongly encourage you to accept the challenges that lie ahead with determination and integrity—always aspiring for excellence.** As part of the next generation of physicians and scientists, you must be committed to improving the health and well-being of the people of Maryland and beyond.

**Academic Units:** In this special issue of *SOMnews*, we celebrate the storied history and major research and medical contributions of the **School of Medicine's Center for Vaccine Development (CVD)**. As the CVD marks its 40th anniversary, we take this opportunity to look back on the numerous milestones made by our faculty. The outstanding investigators of the CVD have devoted their careers to developing new therapeutics for infectious diseases that affect the world's citizens: beginning in 1974, with the development and testing of a live pneumonia vaccine; to the establishment of typhoid fever vaccine studies in Chile in the late 1970s; to the development of an insectary in the 1980s to study malaria; to the licensing of a cholera vaccine in 1994; to the development of an effective influenza vaccine against the 2009 H1N1 pandemic virus.

In addition to the enormous accomplishments of the Center, we also celebrate the lifework of one of the CVD's founders and its current director, **Myron "Mike" Levine, MD, DTPH**. Dr. Levine is a true luminary, recognized nationally and internationally as a preeminent scholar and expert in the field of vaccinology, and boasts an amazing track record for research funding that has supported the mission of the CVD over these four decades. We are indebted to Dr. Levine for his ambitious vision, passion for research, incredible discoveries, dedication to improving medical care for all people, and his consummate and extraordinary leadership over the years.

**Curriculum:** Many of you are aware that a major component of our **Shared Vision 2020** is the **Accelerating Innovation and Discovery in Medicine**

**(ACCEL-Med) Initiative.** We have considered how to more actively involve all our students in a **scholar's research continuum**—beginning when each student enters the School of Medicine, either in the medical, graduate or allied-health programs, and is first exposed to—and becomes an active participant in—academic biomedical research. To crystalize the goals of the individual research programs and begin to recognize and award students who demonstrate extraordinary acuity and productivity in their research projects, we are bringing these collective efforts under one new program: the **Young Brain Initiative (YBI)**. Currently, the School of Medicine offers students a number of various research experiences. These include rotations in basic science or clinical laboratories; the independent projects of the Foundations of Research and Critical Thinking (FRCT) course; and summer research training programs, such as HP-STAR (Health Professions—Student Training in Aging Research Program) or SPORT (Summer Program in Obesity, Diabetes & Nutrition Research Training). More information on the YBI will be forthcoming on the ACCEL-Med web site, but we are extremely excited to launch this new program.

**Leadership Team:** Over the last several months, there have been significant transitions within the Dean's Office. **James B. Kaper, PhD**, was appointed Senior Associate Dean for Academic Affairs in April 2014. As an accomplished scientist, scholar and School of Medicine leader, Dr. Kaper now oversees academic affairs, medical, allied-health and graduate student education, as well as postdoctoral fellowship training. This new role is in addition to his duties as Professor and Chair of the Department of Microbiology and Immunology. He also will continue to "lead by example" and maintain his very active and well-funded research laboratory.



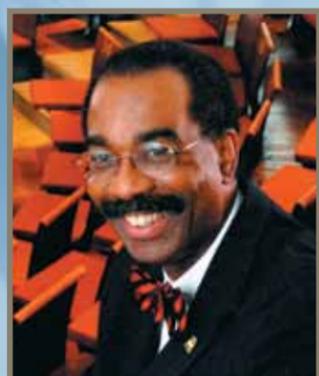
**Terry B. Rogers, PhD**, Professor, Department of Biochemistry and Molecular Biology, has joined the Dean's Office as Executive Director of the Office of Research Affairs. Dr. Rogers was Director of the School of Medicine's MD/PhD Program for 16 years, during which time he grew the program to its current robust size and status, leading the effort to establish the program as an official Medical Scientist Training Program. He brings his extensive experience in research and program management to his new role.

As we look to the months ahead and the major changes we have experienced just within these first few months of 2014, I strongly encourage you to leverage these transitions as opportunities to assess your own progress and make adjustments. In the words of Winston Churchill, **"To improve is to change; to be perfect is to change often."** Change is necessary and should be embraced, lest we fail to make critical adjustments and fall short of our ambitious goals.

In the relentless pursuit of excellence, I am

Sincerely yours,

E. Albert Reece, MD, PhD, MBA  
Vice President for Medical Affairs, University of Maryland  
John Z. and Akiko K. Bowers Distinguished Professor and  
Dean, University of Maryland School of Medicine



“THE OUTSTANDING INVESTIGATORS OF THE CVD HAVE DEVOTED THEIR CAREERS TO DEVELOPING NEW THERAPEUTICS FOR INFECTIOUS DISEASES THAT AFFECT THE WORLD'S CITIZENS.”

# The Center for Vaccine Development Celebrates

# 40 years

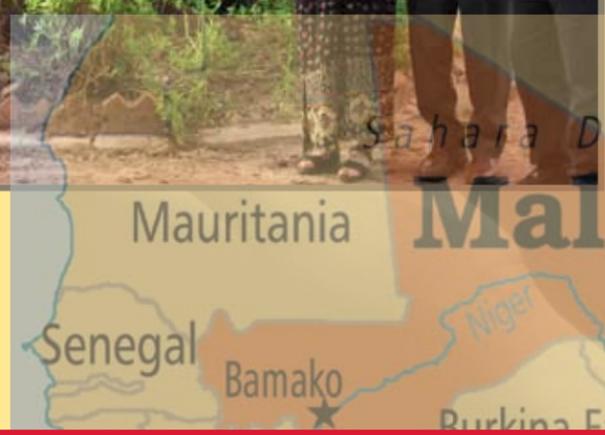
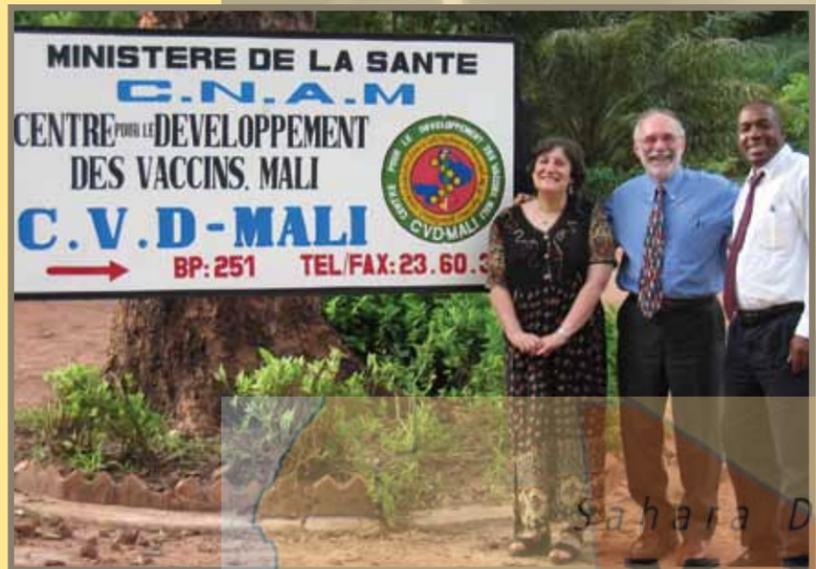
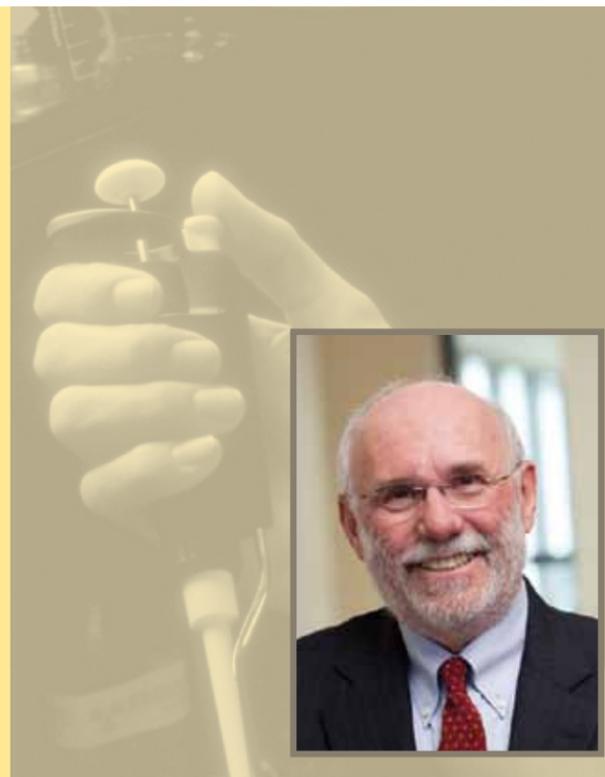
**THIS YEAR** the School of Medicine's Center for Vaccine Development (CVD) is celebrating its 40th anniversary. What started as the Clinical Research Center for Vaccine Development (CRCVD), a clinical vaccine testing unit pilot project with \$250,000 in funding and nine staff members, is now a multidisciplinary academic vaccine development enterprise with scores of millions of dollars in annual funding and facilities and hundreds of staff in several field sites around the globe. Myron "Mike" Levine, MD, DTPH, has been the Director of the CVD from its inception and has overseen this growth and transformation.

CRCVD was initially a one-year pilot project supported by a N01 research contract, with an option for an extension," Dr. Levine explains. "The extension was dependent on us demonstrating that a functioning Research Isolation Ward could be established wherein clinical trials of vaccines that included live vaccines and experimental challenges (e.g., with influenza viruses) could be undertaken in

community volunteers under physical containment."

The CRCVD project was a resounding success, setting the groundwork for the establishment of the CVD as it exists today beginning in 1976. Dr. Levine's vision when writing the first grant application for CVD was to merge research in vaccinology and global health. An important difference between CRCVD and CVD was that the latter could support clinical trials of enteric vaccine candidates designed and constructed at CVD, as well as studies of the pathogenesis of bacterial enteric infections, and there was core funding from the NIH to support related microbiology and immunology laboratory activities. With separate sources of funding, Dr. Levine and his colleagues could also begin to undertake various field epidemiologic studies of diarrheal disease and clinical trials of therapeutic and preventive measures in populations in developing countries, such as Latin America.

CVD Chile was a hotbed for research during the last quarter of the 20th century, but it has diminished greatly in size as Chile has evolved from the developing country it was when Dr. Levine first started working there in the mid-1970s to the industrialized country it is now. "Plummeting young child mortality, extending life expectancy, and increasing gross national income per capita enabled Chile not only to achieve status as an industrialized country but to become the only South American country to be invited into the Organization for Economic Co-



## CVD Timeline 1974 1975 1976 1977 1978 1979 1980 1981 1982 1983 1984 1985 1986 1987 1988 1989

### July, 1974:

Myron "Mike" M. Levine, MD, DTPH, and the late Richard B. Hornick, MD, MACP, establish the Clinical Research Center for Vaccine Development (CRCVD), the precursor of the Center for Vaccine Development (CVD).



Original CVD research isolation ward

### October, 1974:

The CRCVD undertakes its first vaccine study, a clinical trial to assess the safety and immunogenicity of a candidate live *Mycoplasma pneumoniae* vaccine.

### Early 1976:

CRCVD is restructured by Mike Levine and becomes what is now known as CVD.

### Summer 1976:

CVD is designated as a Vaccine and Treatment Evaluation Unit (VTEU) for the first time. With fear of a swine flu pandemic spreading in the U.S., CVD is assigned by NIH to perform safety/immunogenicity studies of pandemic swine influenza and seasonal influenza vaccines in both adults and children, with the ambitious goal to produce sufficient vaccine to immunize more than 100 million people.

### 1978-1989:

Dr. Levine, in conjunction with the late Dr. José Manuel Borgoño, establishes a Typhoid Fever Control Program within the Ministry of Health of Santiago, Chile, and paves the way for



Myron "Mike" Levine, MD, in Chile in 1978



Población in Santiago, Chile 1982

large-scale field trials of Ty21a, a live oral typhoid vaccine. Over these 11 years, CVD carries out four large-scale randomized field trials in ~ 465,000 school children in Santiago to assess the efficacy of different formulations and immunization schedules of Ty21a.

### Late 1970s:

CVD's first oral cholera vaccine, a non-living vaccine consisting of alcohol-inactivated *V. cholerae* 01 administered in combination with glutaraldehyde-treated cholera toxin (i.e., a cholera toxoid) is tested. Also, CVD studies of bacterial pathogenesis in volunteers establish that enterotoxigenic *Escherichia coli* (ETEC) strains that elaborate only heat-stable enterotoxin are capable of causing diarrhea. This result is contrary to the dogma prevalent at the time. Even more momentous is the discovery that volunteers who ingested classical serotype enteropathogenic *E. coli* (EPEC) strains that did not make heat-stable or heat-labile enterotoxins and that did not manifest the ability to invade epithelial cells are nevertheless capable of causing definitive diarrheal illness.

### 1985-1986:

CVD gets deeply involved in studies of one of the first two early malaria vaccines, the Ruth and Victor Nussenzweig vaccine, which consists of 12 amino acid residues (NANP)<sub>3</sub> covalently linked to tetanus toxoid. To carry out malaria challenge studies in volunteers, CVD establishes an insectary, as well as a system to culture *Plasmodium falciparum* in vitro and purify the CVD-1 clone of *P. falciparum* (derived from the NF54 strain).

### 1980s:

CVD expands research on categories of diarrheagenic *E. coli*, including ETEC, EPEC, EHEC (enterohemorrhagic *E. coli*) and EAggEC (enteroaggregative *E. coli*). They also establish a model of shigellosis and undertake the evaluation of candidate *Shigella* vaccines made by the Department of Defense. The

## Primary Faculty in the CVD

Eileen Barry, PhD, Professor  
 Andrea Berry, MD, Assistant Professor  
 William Blackwelder, PhD, Professor  
 William Blattner, MD, Professor  
 James Campbell, MD, Associate Professor  
 Wilbur Chen, MD, Assistant Professor  
 Alan Cross, MD, Professor  
 Robert Edelman, MD, Professor  
 James Galen, PhD, Professor  
 Shannon Takala Harrison, PhD, Assistant Professor  
 James Kaper, PhD, Professor  
 Karen Kotloff, MD, Professor  
 Miriam Laufer, MD, MPH, Associate Professor  
 Matthew Laurens, MD, MPH, Assistant Professor  
 Myron Levine, MD, DTPH, Professor  
 Kirsten Lyke, MD, Associate Professor  
 Monica McArthur, MD, PhD, Instructor  
 Rosangela Mezghanni, PhD, Assistant Professor  
 Dilruba Nasrin, MBBS, PhD, Assistant Professor  
 Myaing Nyunt, MD, PhD, MPH, Assistant Professor  
 Marcela Pasetti, PhD, Professor  
 Christopher Plowe, MD, MPH, Professor  
 Raphael Simon, PhD, Assistant Professor  
 Jennifer Snyder, PhD, Instructor  
 Marcelo Szein, MD, Professor  
 Milagritos Tapia, MD, Assistant Professor  
 Sharon Tennant, PhD, Assistant Professor  
 Franklin Toapanta Yanchapaxi, MD, PhD, Research Associate  
 Mark Travassos, MD, MSc, Instructor  
 Rezwanul Wahid, MBBS, PhD, Assistant Professor  
 Yukun Wu, PhD, Research Associate

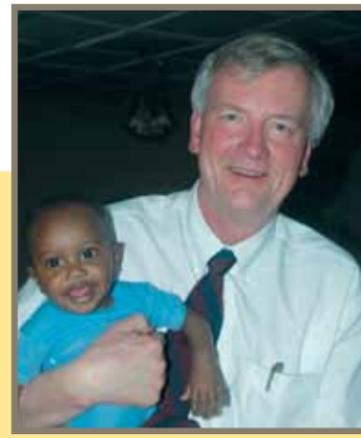
operation and Development (OECD)," says Dr. Levine, who credits, in part, a series of collaborative public health research programs carried out by CVD and the Ministry of Health of Chile for this change.

Today, the Republic of Mali in West Africa is an important area of focus for the Center. "CVD-Mali has two components," Dr. Levine explains. "One focuses on endemic and epidemic infectious diseases, mainly affecting young children. This component of CVD-Mali represents a partnership between the Ministry of Health of Mali and the University of Maryland, Baltimore. The other component is the Bandiagara Malaria Project, run by CVD's Malaria Group, which works in a hyper-endemic area of malaria around Bandiagara."

Malaria and other diseases that mainly afflict populations in the developing world and for which there do not exist substantial markets in industrialized countries have historically not been a priority for "Big Pharma" vaccine manufacturers. CVD has helped to fill this void, focusing on enteric diseases (cholera, typhoid & paratyphoid fever, *Shigella*, ETEC), malaria and Group A *Streptococcus pyogenes*. CVD has also worked on ways to administer vaccines without injection (mucosal vaccines) or with fewer injections (combination vaccines and single-dose vaccines) and extending the targets (vaccines for early infancy, the elderly and pregnant women). CVD has been a leader in introducing

pneumococcus, *Haemophilus influenzae* type b and influenza vaccines in West Africa. Biodefense vaccines were a major focus during the decade after 9/11/2001.

The Center is particularly devoted to infectious diseases that affect children in less-developed countries. To gather information on the burden of diarrheal diseases, CVD over-



saw the Global Enteric Multicenter Study (GEMS), the largest, most comprehensive study of the burden and etiology of childhood diarrheal diseases ever conducted in developing country settings. The Bill & Melinda Gates Foundation funded that historical effort. CVD faculty and staff also consult with international agencies such as the World Health Organization, the Agency for International Development, The World Bank, and the GAVI Alliance (the Global Alliance for Vaccines and Immunization), as well as with individual governments and industry.

A considerable portion of funding for the CVD comes from federal agencies, particularly the National Institute of Allergy and Infectious Diseases (NIAID). Recent major grants from NIH include: competitive renewals of the Vaccine and Treatment Evaluation Unit (VTEU) (Karen Kotloff, PI), a 10-year N01 contract with potential funding up to \$135 million, and of the Cooperative Center for Human Immunology (CCHI), a 5-year \$13.5 million U19 grant (Marcelo Szein, PI); and an award for a Center of Excellence for Translational Research (CETR), a 5-year \$25 million U19 grant (Mike Levine, PI).

Funding for training also comes from federal sources. The CVD has trained generations of scientists in the field of vaccinology, a term that was rarely used when CVD started. CVD was the first to receive a T32 Training Grant in Vaccinology from the NIH (that grant is now in its fourth cycle). T32 grants develop or enhance research training opportunities for individuals selected by the institution.

These various training grants have

helped recruit outstanding scientists to CVD, some of whom have stayed on as faculty. Others have gone on to teach vaccinology at other schools; work for government agencies such as the CDC, the FDA, the Department of Defense, and NIH; and many are working around the world, developing and testing vaccines and carrying on this life-saving work as a legacy to their mentors.

CVD is now a top "brand" in the world of vaccinology, thanks to the hard work of Dr. Levine and the expectation of excellence he has cultivated during his 40 years of leadership. Yet now Dr. Levine is preparing to step down as Director in December, to become Associate Dean for Global Health, Vaccinology and Infectious Diseases, as well as spend more time in the field. "I like the field work of vaccinology that puts mud on my boots and that allows me to translate our basic science research to clinical applications," he declares with a smile.

Upper left: Myron M. Levine, MD, DTPH  
 Left: Karen Kotloff, MD, and Myron M. Levine with Samba Sow, MD, MS, Director of the CVD Mali site  
 Below: Kirsten Lyke, MD out in the field  
 Top right: William Blattner, MD



late 1980s sees the initiation of research to develop attenuated strains of *Salmonella* Typhi to serve as single-dose live oral typhoid vaccines and as live vectors to deliver foreign antigens to the immune system. During this decade, CVD also finds that attenuated *Vibrio cholerae* O1 strain CVD 103 is well-tolerated yet highly immunogenic and protective.

When investigator James Kaper, PhD (now Chair of the Department of Microbiology & Immunology)



introduces a gene-encoding resistance to mercury ions into the hemolysin A locus of CVD 103, the vaccine strain CVD 103-HgR results. CVD 103-HgR is found to be well-tolerated, immunogenic, and protective with a single oral dose, so a clinical development

program to obtain licensure for this vaccine strain is initiated.

## 1994:

Vaccine strain CVD 103-HgR is licensed by the Swiss National Regulatory Agency as a single-dose live oral cholera vaccine for travelers and shortly thereafter by the National Regulatory Agencies of Australia, New Zealand, Canada and several other countries, as well. Clinical trials in Asia, Latin America and Africa document the safety and immunogenicity of CVD 103-HgR. It is also during this time that CVD acquires the first cycle of their T32 Training Grant in Vaccinology.

## 2000-2010:

CVD is chosen to serve as the Coordinating Institution for the Middle Atlantic Regional Center of Excellence for Biodefense and Emerging Infectious Diseases Research (MARCE). The large MARCE-1 and MARCE-2 grants

(~ \$100 million) support an array of research projects at CVD and provide opportunities for interactive research with investigators at other institutions.

The Bill & Melinda Gates Foundation gives Dr. Levine and CVD a grant for \$20.4 million to develop a new measles vaccine that could be effectively administered to infants < 6 months of age (when current live measles vaccines are poorly immunogenic). The Foundation also gives Dr. Levine an initial \$28 million of what will ultimately be more than \$45 million to carry out what comes to be known as the Global Enteric Multicenter



CVD Mali clinic

Study (GEMS), which measures the burden and etiology of diarrheal disease in children < 60 months of age in four sites in sub-Saharan Africa and three in South Asia.

Le Centre pour le Développement des Vaccins du Mali (CVD-Mali) is established as a collaborative venture between the CVD and the Ministry of Health of Mali, with initial funding from the Rockefeller Foundation and the Bill & Melinda Gates Foundation.

## 2007:

Christopher Plowe, MD, MPH, is named a Howard Hughes Medical Institute



(HHMI) Investigator in Patient-Oriented Research, the first from the School of Medicine to be funded by this prestigious institution.

## 2009:

Marcelo Szein, MD, successfully competes for a Cooperative Center for Translational Research on Human Immunology and Biodefense (CCHI)

grant. In the arena of human immunology research, CCHIs are highly prestigious and competitive, and this grant adds sophistication to immunology research on vaccines at CVD.

## 2013:

The National Institute of Allergy and Infectious Diseases renews designation for CVD and eight other research centers throughout the United States as Vaccine and Treatment Evaluation Units (VTEUs). The current CVD VTEU is led by Karen Kotloff, MD.



# Lessons in Life and Medicine

Garnered by Medical Students While Abroad

► BY MARGEAUX CORBY, MS-III

Through a variety of global projects, medical students at the University of Maryland are already becoming practitioners in the advancement of international medicine.

While in Burma studying drug-resistant malaria, third-year medical student Christian Larsen would take a cab to the Department of Medical Research and begin work. Then the power would go out. When it eventually flickered back to life, he would begin again. "It required you to be resilient and adaptable," Larsen says. "It teaches you to learn to work with circumstances you have."

This was a good lesson when working with a disease as unpredictable as malaria. "You take a virus, and a quadrivalent vaccine is good enough, it's going to cover four of the most prevalent strains, and the virus won't change quickly enough since it has a limited repertoire of genes," Larsen explains. "If you take a protozoan parasite like malaria, it is complex, multicellular, and can make a lot of broad changes to its genome and continue to thrive. Malaria required us to use novel strategies in vaccine development."

Kristin Lohr, a third-year medical student who spent six weeks in Malawi surveying rural health centers' capability of providing care for expectant mothers, was as impressed as Larsen by the resourcefulness of clinicians practicing with limited means. "They have a better grasp of clinical medicine than we do here," she said. "They really have to listen to what patients are saying

since they don't have CT scans or imaging studies. Sometimes they didn't even have working blood pressure cuffs." Classmate Sarah Britz also worked in Malawi and saw the consequences of unreliable transportation, where laboring mothers had to ride bikes to the nearest health center. "It really opened my eyes to the idea of global health care inequality," she said. "It's something you hear a lot about but you don't really grasp the extent of it until you're there and actually see what it means."

The School of Medicine's international research and clinical work is in the spotlight as the Center for Vaccine Development celebrates its 40th anniversary this year. Our medical students have met this challenge by traveling to cities in Latin America, Southeast Asia and rural districts in Africa, as well as participating in domestic efforts to help the global community. The Global Health Interest Group (GHIG) is a student-run program that serves as a forum for medical students to connect with mentors working internationally, to increase awareness of global health issues.

This year GHIG has worked with other professional schools to develop a new scholarship promoting interprofessional work abroad and has created a panel on international work being done locally. Crystal Bae, second-year medical student and president of GHIG, has spearheaded these efforts. She also volunteers for the International Rescue Committee, where

she teaches health workshops to English proficient refugees. "We talk about preventative health issues, like how to read a nutrition label," Bae said. In the future, she plans to start home

**The Global Health Interest Group (GHIG) is a student-run program that serves as a forum for medical students to connect with mentors working internationally, to increase awareness of global health issues.**

visits to refugees struggling with multiple medications that require close monitoring or have complex administration schedules. "Everyone has the right to a lead a

healthy life and have access to care in medicine," she said. "No matter what country or city you're in."

Students who have gone abroad emphasize that lessons learned working in international medicine continue to influence their training at home. "It makes me think, 'How I am learning clinically?'" Lohr said. "In my third year, I rely so much on tests and things I can order. But would I do for this patient if I were in Malawi?"



Kristin Lohr in Malawi

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▲ E. Albert Reece, MD, PhD, MBA, Vice President for Medical Affairs, University of Maryland, and Dean, University of Maryland School of Medicine ▲ Chris Hardwick, Executive Editor ▲ Caelie Haines, Managing Editor  
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▲ Submitting information to SOMnews: Please email your submission six weeks prior to the month you wish to see your submission included to Caelie Haines, Public Affairs Manager, at [chaines@som.umaryland.edu](mailto:chaines@som.umaryland.edu).  
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UNIVERSITY of MARYLAND  
SCHOOL OF MEDICINE  
655 West Baltimore Street  
Baltimore, Maryland 21201-1559



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