THE SPECTROGRAPH

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Laser Biomedical Research Center
George R. Harrison Spectroscopy Laboratory
Massachusetts Institute of Technology

Peter So, Professor of Mechanical and o Biological Engineering, Directs the LBRC

Welcome and Update from LBRC Director Peter So

This is the first issue of our newsletter *The Spectrograph* since 2010. The past six years have been a time of transition in laboratory leadership and program. Restarting the newsletter gives me the chance to introduce myself and bring you up to date on the research accomplishments of the SpecLab and its Laser Biomedical Research Center (LBRC). Many of you have had a much longer

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In this newsletter (click on it)

Jun Ye, 2016 Lord Lecturer: The Control of Light for Spectroscopy

by Charles H. Holbrow

"MIT is my favorite school where I did not get into graduate school," Jun Ye told an amused audience as he began his 2016 Lord Lecture: "Control of Light for Spectroscopy." Instead he got his Ph. D. in 1997 under Jan Hall (2005 physics Nobelist) at Colorado, did a post-doc at CalTech under Jeff Kimble, and returned to Boulder in 1999 where he is now Professor of Physics at the University of Colorado and Fellow at JILA and NIST.

In his notably creative and imaginative research Jun Ye has made the strontium optical clock laser and the frequency comb key

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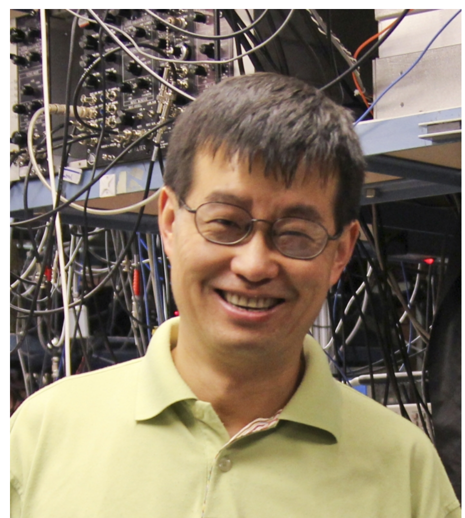

Jun Ye, NIST and JILA Fellow and University of Colorado Professor gave the 2016 Lord Lecture

New Company to Use LBRC Raman Technology to Guide Epidural Needles

by Jeon Woong Kang

In 2014 T. Anthony Anderson, Jeon Woong Kang, Peter So, Ramachandra Dasari, and Cheryl Campbell founded a new company, Biosight LLC (now Medisight Corp), to use LBRC technology to reduce injury that can occur when epidural needles are inserted into a patient's spinal region. To administer epidural anesthesia, a doctor pokes a 6-inch long needle through six layers of different tissues that protect the spinal cord and then inserts a catheter into the epidural gap.

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Gabriela Schlau-Cohen to join LBRC Core Faculty

by Charles H. Holbrow


Gabriela Schlau-Cohen, MIT Assistant Professor of Chemistry

Next year Gabriela Schlau-Cohen will become one of four new members of the LBRC core faculty. Since joining the MIT Department of Chemistry in January 2015, she has been vigorously developing her research program. She uses single-molecule and ultrafast spectroscopies to study energetic and structural dynamics of biological systems. By developing new methods for measuring dynamics on single proteins and by merging optical spectroscopy with model membrane systems, she seeks to advance understanding of membrane proteins, including their role in photo-synthetic light harvesting.

A lively and engaging person, she first became interested in physical chemistry when "an amazing chemistry teacher" in the tenth grade described the wave-particle duality of electrons. The topic fascinated her, and as an undergraduate at Brown University she majored in chemical physics; she liked that this major substituted physics courses for organic chemistry courses. At Brown University, she and Conor Evans (who will also join LBRC next year) did quantum mechanics homework together.

After graduating from Brown she did not go directly to graduate school. Instead she worked for three years in New York City as a political organizer for the Working Families Party. In 2006 she returned to science and entered UC Berkeley's graduate program in physical chemistry where she completed her Ph. D. in 2011 under the supervision of Graham Fleming (SpecLab's 2007 Lord lecturer). After a three-year post-doctoral fellowship at Stanford (supervised by W.E. Moerner), Gabriela came to MIT.

Gabriela will bring to LBRC

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We Will Tell Ali Javan's Story

by Poorya Hosseini


Poorya Hosseini and Sona Hosseini visit Ali Javan in California

Ali Javan, a remarkable man and a notable physicist, was born in Tehran in 1926 of Azerbaijani parents. He came to America in 1948 and took graduate courses at Columbia where, under the supervision of Charles Townes, he received his Ph. D. in 1954 (he never obtained a bachelor's or a master's degree). At Bell Labs in 1960 he co-invented the gas laser. In 1961 he joined the MIT faculty and over a long career did creative, inventive, insightful research on

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the use of spectroscopy at the size scale of single proteins. At large scale LBRC already uses spectroscopy to develop instruments with clinical applications. These applications at the large scale are made possible by results from LBRC's spectroscopic studies of medium-scale systems of tissues, cells, and organelles. Now with her refinements of FRET (Förster Resonance Energy Transfer), a spectroscopic ruler, Gabriela can measure the spacing between interacting proteins and how this spacing varies on the time scale of microseconds. Gabriela's lab uses this tool to identify the mechanisms by which membrane proteins function. Membrane proteins are ~60% of drug targets, and understanding how they work may increase the speed and efficacy of drug development.

Her work with optical spectroscopy is well recognized: In 2015 she received the Smith Family Award for excellence in biomedical research; in 2016 she received a Beckman Young Investigator Award and also was named a CIFAR-Azrieli Global Scholar. Her active research program — which includes tracing energy transfers within proteins, her enthusiasm for her science, and her vigorous teaching show that when she joins LBRC next year there will be energy transfer at the large scale as well as at the small.

Peter So (from pg. 1)

association with the SpecLab than I who began working in it only five years ago. As a researcher in the biomedical optics area, I of course knew about the work and accomplishments of the late Dr. Michael Feld and the MIT SpecLab. When I joined MIT in 1996 as a junior faculty member in the Department of Mechanical Engineering, and later with a dual appointment with the Department of Biological Engineering, two of the leaders in the photonics field that I first met at MIT were Michael and Dr. Ramachandra Dasari. I still remember that Ramachandra kindly took me for a laboratory tour talking with researchers developing chemometric algorithms for cancer diagnosis and for glucose detection in blood. And one of the first seminars that I gave at MIT was in the Modern Optics Seminar series at Michael's kind invitation. I am still grateful that these senior scientists took their time to meet with me and make me feel at home at MIT.

My involvement with Michael and Ramachandra increased over the years. Besides regularly attending the Modern Optics Seminars and the Lester Wolfe Workshops, I have enjoyed serving on the scientific advisory committee of the Laser Biomedical Research Center, LBRC, an NIH P41 research resource that placed SpecLab multi-disciplinary biophotonics research under one roof. For over a decade I looked forward to these yearly meetings. They allowed me to learn about new biophotonics techniques that I wasn't familiar with and also how these techniques can impact biomedical practices. More important, these meetings provided me the opportunity to meet many talented graduate students, postdoctoral researchers, and visiting scientists who have worked in LBRC; many are still good friends today. One of greatest achievements of 30 years of LBRC existence is the training of several generations of leading scientists in the biophotonics field.

Although Michael's health was a challenge for several years, it was still a shock when he died in 2010. During the subsequent transition period, Ramachandra returned to MIT from retirement. An urgent task at that time was securing funding renewal of the LBRC, a financial pillar of SpecLab activities. In several meetings, the late Dr. Bob Silbey, who was then serving as the director of SpecLab, asked Ramachandra, Dr. Moungi Bawendi, Dr. Andrei Tokmakoff, and me to lead this renewal effort. As most of us had never managed an NIH center previously, it was a big learning experience for all of us. Fortunately, our effort was successful. With the departure of Andrei to the University of Chicago, LBRC has been operating with me as

Director and Moungi and Ramachandra as Associate Directors for the last four years.

The philosophy of our new leadership team has been to preserve the key intellectual capital in LBRC and to bring in new members with complementary expertise. Under Michael and Ramachandra's guidance, LBRC became a world leader in label-free biophotonics techniques with particular strengths in Raman methodology and in interferometric imaging.

With Ramachandra returned from retirement, the LBRC Raman group has remained productive throughout the transition. Most recently they have developed Raman and diffusive reflectance methods for grading breast lesions associated with microcalcification, and they have developed a new algorithm for transdermal glucose sensing that has enabled accurate blood glucose concentration determination for several days after only one blood drawing for calibration.

For interferometric imaging techniques, I have worked with Dr. Zahid Yaqoob to preserve the expert in-house knowledge in this area and to strengthen the phase subgroup. The revitalized phase subgroup is now making good progress. They have used quantitative phase microscopy to identify biophysical markers for sickle cell diseases that may be more effective diagnostics than commonly used biochemical markers. They have also developed reflection quantitative phase microscopes based on speckle correlation or confocal detection to study the biomechanics of membrane nuclei that are implicated in diseases such as progeria and cancer metastasis.

Moungi and I have also brought to LBRC our expertise in fluorescence instrumentation and contrast agents. We are developing a highly parallelized super-resolution imaging technique based on point spread function engineering that may make it possible to map the brain's circuit diagram on the synaptic level. We are also using novel quantum dots synthesized by Moungi's group and emitting up to 1700 nm to develop imaging methodologies in the short-wave infrared region. These new quantum dots not only allow deeper imaging by exploiting a spectral region where tissue scattering is minimal but, as developed by Moungi, they can also sense their biochemical environment. For example, they can reveal the oxygen distribution that has important effects on the metabolism of diseases such as cancer.

We are in the fourth year of our funding cycle and preparing the next renewal. The exciting news is that we will add four senior investigators to LBRC in addition to Moungi, Ramachandra, and me. Dr. Gabriela Schlau-Cohen from the department of Chemistry has agreed to join us bringing in additional expertise in single molecule spectroscopy. Dr. Zahid Yaqoob has been a leader of our phase group for many years, and we want to recognize his contributions by promoting him to be a senior investigator in the center. To extend the impact of LBRC and SpecLab we will work with two investigators in partnering institutions. Each will bring us complementary expertise: Dr. Ishan Barman of Johns Hopkins University will bring his expertise in Raman and surface enhanced Raman spectroscopy; Dr. Conor Evans of the Wellman Center will bring his expertise in nonlinear Raman techniques and join LBRC as a senior investigator, further strengthening the already important collaboration between Wellman and LBRC.

With the research activities of LBRC back on track after a major transition, we thought that it was time to bring back *The Spectrograph*. It has for many years linked us to friends of the MIT SpecLab and provided communication among faculty, students, and researchers who have been associated with this venerable MIT institution.

It is good to see the newsletter once again helping to build our community. If you have questions or wish to learn more about the LBRC and its work, please contact me. As Director I will be happy to respond. You can easily reach me by sending an email to cbrooks@mit.edu.

tools in his effort to achieve 1 mHz optical linewidth and greater than 100 s coherence time for light from the infrared (IR) to the extreme ultraviolet (XUV). In his Lord Lecture Jun Ye described progress toward this goal and examples of how exceptional resolution and stability are advancing spectroscopy.

Bob Field, introducing Jun Ye, told a large and attentive audience that Jun Ye's beautiful experiments and his great talent have been recognized by many honors, including the I. I. Rabi Prize of the American Physical Society, election to the National Academy of Sciences, and a Presidential Rank Award. Bob, pointing out that Jun Ye's talent was early evident when he developed heterodyne spectroscopy to give both high resolution and high sensitivity, particularly admired Jun Ye's acronym for this technique: NICE-OHMS.

Jun Ye recalled Bob's 1997 remark that NICE-OHMS sees trees but not the overall picture, i.e., not the forest. "That remark was made before the comb, but when the comb came around, I easily remembered Bob's remark: 'Could you please combine high resolution and high sensitivity with being able to see the entire forest?' And that's what comb spectroscopy has brought us." This was the central message of Jun Ye's lecture.

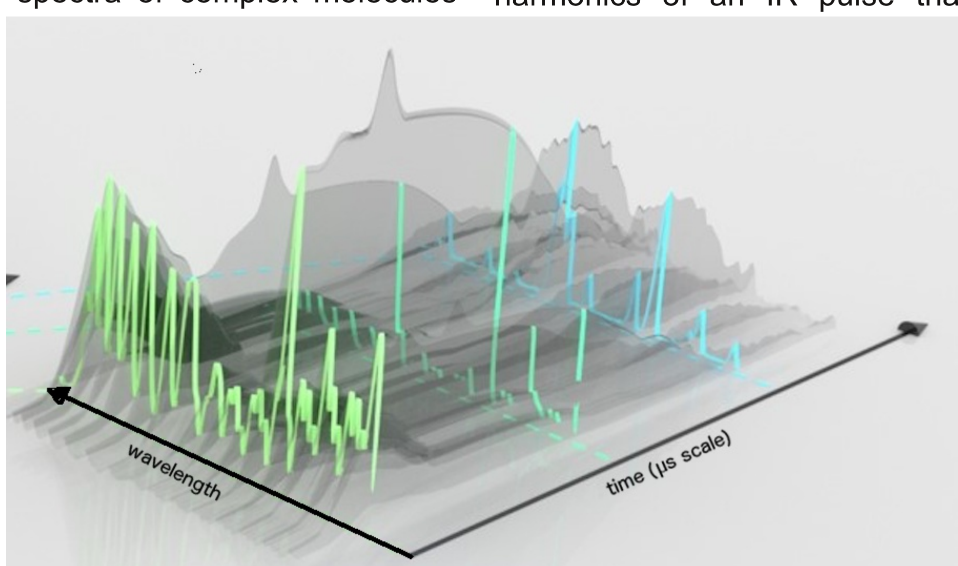
Noting improvements in resolution in successive factors of a million from Newton's time, he brought us to today when a laser based on "my favorite atom—strontium" and a cooled single-crystal silicon cavity gives femtosecond time resolution and light pulses that retain phase coherence for over a minute.

Combining such lasers with the frequency comb revolutionizes spectroscopy. The frequency comb is a remarkable tool for the control of light, and Jun Ye skillfully reviewed the physics that has made it possible (and which won his mentor Jan Hall his Nobel Prize). The comb generated from a mode-locked ultra-stable laser becomes in effect millions of separate continuous-wave lasers acting simultaneously and in phase on a sample.

The combination of an ultra-stable high-resolution laser and frequency comb advances spectroscopy in remarkable ways. One particularly notable advance is the vastly improved ability to study spectra of complex molecules over a broad band of frequencies. The combination of such good spectral and time resolution makes it possible to untangle complicated molecular kinetics. Jun Ye showed how he and his colleagues were able to understand the kinetics of the carboxyl radical HOCO by observing the spectroscopy of DOCO in 10 μs steps of time as it forms as an intermediate species in the process of $CO + OD \longrightarrow CO_2 + D$. Understanding HOCO is important because it plays a crucial role in atmospheric chemistry and combustion.

Jun Ye and his students have extended the frequency comb into the extreme ultra-violet (XUV). This notable advance offers a prospect for high-resolution tests of QED, enhances the capability of looking for variation of fundamental constants, makes possible direct excitation of some nuclear transitions, and opens to spectroscopy an unexplored realm from 10 to 100 nm.

They make XUV light from the harmonics of an IR pulse that



Successive spectra at intervals show evolution of DOCO as the reaction progresses strikes an atom and produces an electric field strong enough to tilt the Coulomb barrier so that electrons tunnel out of the atom. The atom's recapture of these electrons makes a train of harmonic pulses that extends into the XUV. Applying a sequence of coherent IR pulses 10 ns apart gives a high-resolution comb within each harmonic. To get sufficient energy in each line of the comb requires 10 to 100 kW of laser light. They achieved this with a 1-W laser and a build-up optical cavity. The coherent summation of a succession of pulses yields tens of kW in the cavity. To their delight they found that at 10-ns repetition rate the coherence and resolution of the 1-W IR laser are retained out to the 17th harmonic, and 1 mW average power per XUV harmonic was demonstrated. "Nature was very kind to us."

Jun Ye's lecture was rich in interesting detail and broad in scope. To learn more about topics not included in this brief article (e.g., his candidate for ruler of the Universe), you can view his lecture at http://lbrc.mit.edu/mos-seminar-videos/.

It was a fine lecture, and Bob Field expressed for all the audience and SpecLab people our gratitude, admiration, and pleasure for Jun Ye's outstanding contribution to the Lord Lecture tradition of excellence.

New Start-Up (from pg. 1)

Doctors can't see the path of the needle, but they can tell it has reached the gap by feeling decreased resistance as they push the needle in. If a doctor misjudges the feeling and the needle goes too far, it can injure the spinal cord. Given that the procedure is blind — the doctor is groping in the dark — it is not surprising that injury occurs in about 10% of the 13 million epidural procedures performed each year. On average it costs an additional $2000 to treat such an injury; this is an additional cost of $200 per epidural needle placement. As a practicing pediatric and adult anesthesiologist, Dr. T. Anthony Anderson of the MGH Department of Anesthesia frequently inserts epidural catheters via epidural needles for post-operative pain control. In the spring of 2014 he came to the MIT Laser Biomedical Research Center (LBRC) and found there

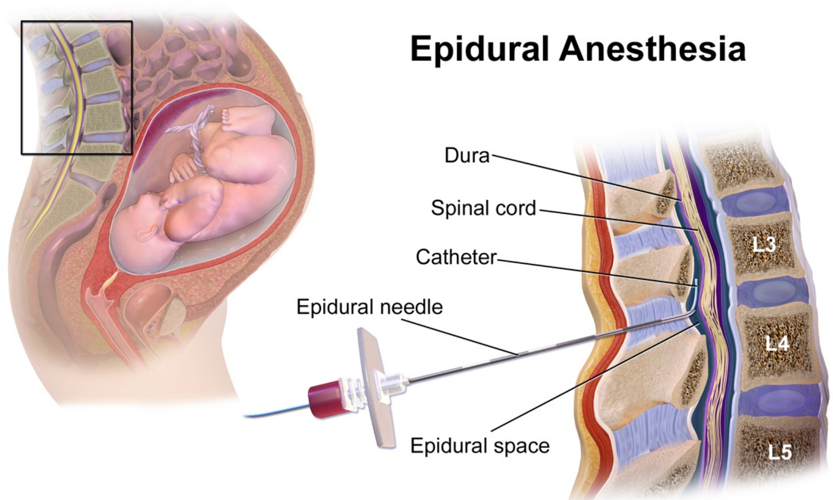


Image by Bruce Blaus on Wikipedia

a technology to increase the safety and accuracy of this medical procedure.

Over the past decade LBRC scientists have used spectroscopy to distinguish different types of tissue from each other. They have used spectroscopy to detect atherosclerosis. And by using spectroscopy to distinguish tumors from healthy tissue they have been able to diagnose various cancers. The diagnostic accuracy of distinguishing diseased from healthy tissues by spectroscopy is approximately 90%. Because different tissue layers have different chemical compositions, spectroscopic identification of different distinct tissues is a simpler problem than cancer diagnosis. We have shown in an ex vivo swine model that all eight tissue layers that an epidural needle might meet --- skin, fat, muscle, supraspinous ligament, ligamentum flavum, epidural fat, dura mater, and spinal cord --- can be clearly distinguished with 100% accuracy using Raman spectroscopy. Not only does our miniature probe solve this clinically important problem, it does so economically. We think our probe can be manufactured for approximately $20. Then for $20 per needle placement, doctors can eliminate the $200 average extra cost needed to deal with needle-related complications. Thus, there is likely to be a good market for our miniature Raman probe.

Responding to this opportunity, in 2014 we filed a utility patent on a miniature Raman probe that can be integrated into currently used epidural needles, and we founded Biosight, LLC (recently converted to Medisight Corp). We entered the 2014 MIT 100K Entrepreneurship Competition. This MIT-supported, student-run program stimulates entrepreneurial effort by a three-stage competition. We were selected as an MIT 100K Pitch finalist and a Launch semi-finalist. Reviewers for MIT 100K suggested that we build a working prototype and collect live animal data. To do this we have obtained funding from the National Science Foundation Small Business Technology Transfer Program (STTR Phase I), and we are developing a prototype device and will perform live animal experiments this fall.

MIT is very supportive of our endeavor. MIT's Translational Fellows Program (run by RLE) provides its post-doc fellows a day-a-week education on how to launch a business from laboratory technology. The MIT Venture Mentoring Service provides practical advice on patent licensing, accounting details, and business development. The MIT Innovation Initiative has provided Medisight an office space in Kendall square.

Medisight's potential market is larger than just epidural needle placement. There are many other medical procedures from which complications occur during blind or semi-blind needle placement. We plan to develop our technology so that it can be used to decrease procedural complications and improve accuracy in other clinical applications including cancer biopsies and joint injections. The company has a bright future.

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THE LASER BIOMEDICAL RESEARCH LABORATORY

Director: Peter So
Associate Directors:
Moungi Bawendi
Ramachandra R. Dasari

The LBRC is a national research resource center in laser biomedicine supported by the National Institute of Biomedical Imaging and Bioengineering of the National Institutes of Health. The LBRC's mission is to develop basic scientific understanding and new techniques that advance clinical applications of lasers and spectroscopy.

MODERN OPTICS AND SPECTROSCOPY SEMINAR
FALL 2016

Some seminars remain to be scheduled. Titles and a complete final schedule will be available at http://lbrc.mit.edu/category/seminars/modern-optics-and-spectroscopy-seminar/ The seminars are held 12:00-1:00 pm in the Grier Room (34-401)

Oct. 18, 2016	Christy Landes, Rice University
Nov. 1, 2016	Bruce Tromberg, University of California, Irvine (Dasari Lecture)
Nov. 15, 2016	Martin Zanni, University of Wisconsin, Madison
Nov. 22, 2016	Vadim Backman, Northwestern University
Nov. 29, 2016	Poorya Hosseini, MIT

The Lester Wolfe workshop will be held on Tuesday, November 1, 2016. The following speakers are confirmed:

Robert Huber, Universitat zu Luebeck
Frank Wise, Cornell University
Andy Yun, Harvard Medical School/MGH

Discovery Question: What happens when you click on ?

Javan Story (from pg. 2)

quantum physics, lasers, and spectroscopy. He moved to emeritus status in 1997. To make his achievements and career more widely known, I have recruited a team of talented young Iranian artists, writers, and scientists to produce a video documentary of his life and accomplishments.

I got the idea for the documentary after I first met Professor Ali Javan in January 2013 at a farewell dinner for a SpecLab colleague. In the following months, I learned more about Javan from people who had been associated with him during his MIT years. Realizing how little young scientists and the general public know about him, I launched a project to make a documentary movie of his life, career, and the story of the gas laser.

The initial work has been done in collaboration with the Safarani sisters. They are Iranian twins, currently pursuing master's degrees from the College of Art, Media and Design at Northeastern and the School of the Museum of Fine Arts, Boston. They work primarily in painting and video and have shown their work widely in the United States and internationally. “Ali Javan has a strong and unique personality. By using our art to share his life story and take others on this journey, we seek to respond to his profound humanity and his sacrifices as part of our responsibilities as artists,” say

The Safarani sisters bring artistic talent fo the project

the Safarani sisters.

Our project is under way. We have been interviewing people who can tell us Prof. Javan’s life story. Our activities have been partially supported by the Iranian Studies Group (ISG) at MIT, and now we are raising the funds necessary to move to full production and complete the project.

We recently had a great addition to our team, Dr. Sona Hosseini. I met Sona during a recent visit to California. We were brought together, one might say, as though by unknown forces in the universe. At a dinner party in beautiful Los Angeles she asked why I was visiting there; I told her I had come mainly to see Prof. Javan. The moment I mentioned that name, she lit up with excitement and had a lot to share with me. She had been fortunate enough to get to know Charles Townes, who was Prof. Javan's thesis adviser, knew Ali Javan very well, and shared many stories with her.

Sona is an inspirational person with a passion for science. She fell in love with astronomy during her first-grade elementary school trip to the NASA Space Center in Houston, and astronomy became the center of her personal and professional activities. Ever since, she has worked with some of the world’s best scientific leaders and has led many instrumentation projects for astrophysics and planetary studies. In 2015 she joined Jet Propulsion Lab. She is now a member of our team, and we are excited to have her passion, expertise, and support.

Bahar Royaee and Ehsan Moghaddasi recently joined the project. Ehsan is a graduate of University of Tehran’s dramatic arts department, and, interested in the art of filmmaking, he is studying part time at Boston University’s film school. Bahar is a music composer recently graduated from Berklee College of Music. She has composed music for many plays and performances in the Boston area. She is currently continuing her studies in composition at Boston Conservatory.

We have launched a webpage that introduces our project and our fundraising goals. It is at: http://javanproject.com/.