University of Colorado School of Medicine
Medical Scientist Training Program and
MSTP Student Council Present

The Annual MSTP Retreat
2019
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Thank You to our Sponsors
Schedule of Events

11:45-12:15  Box Lunch Available
12:15-12:30  Welcome: Student Council Leadership
12:30-1:30  Alumnus Keynote Speaker - Benjamin Young, MD, PhD
            “Ending a Plague: Meandered Lessons in Compassion, Humanism and HIV Medicine”
1:30 - 2:30  Workshop - Anne Libby, PhD “How to Negotiate”
2:30-3:00  Networking and Coffee
3:00-4:00  Student Oral Presentations

3:00-3:15: Meagan Chriswell, Cross-reactivity between autoantibodies and mucosal bacteria in pre-clinical rheumatoid arthritis: evidence of molecular mimicry driving disease initiation?

3:15-3:30: Harry Park, Understanding the mechanism of bone marrow stromal cell-mediated protection of FLT3-ITD AML from FLT3-targeted therapy

3:30-3:45: Isabel Fernandez, A Novel Human IL2RB Mutation Results in T and NK cell-driven Immune Dysregulation

3:45-4:00 Aaron Bowen, Local biosynthetic trafficking of synaptic proteins in neuronal dendrites breaks the rules of cell biology
4:00-5:00  Poster Session and Coffee

5:00-6:00  Student Oral Presentations

5:00-5:15: Ashley Denney, *Impact of folding kinetics on the dimerization and dominance of tumor-derived p53 mutations*

5:15-5:30: Elijah Christensen, *Inferring sleep stage from local field potentials recorded in the subthalamic nucleus of Parkinson's patients*

5:30-5:45: Michael Nash, *Maternal western-style diet persistently alters bone and liver myeloid cell development and function in a non-human primate model*

5:45-6:00: Hannah Scarborough, *Determinants of career outcomes of MSTP students at the University of Colorado (1985-2015)*

6:00-6:10  Excellence in Service Award

*Presented by Elizabeth Bowen*

6:10-6:30  State of the Program Address

*Delivered by Dr. Arthur Gutierrez-Hartmann*
Please Join For The
Official Unofficial Post-Retreat Celebration
At Infinite Monkey Theorem
In the Stanley Marketplace

Stanley Marketplace is approximately 5 minutes from campus by car
2501 Dallas St, Aurora, CO 80010

Head East on Montview Blvd for 1 mile, turn right on to Ironton St and
left onto 25th Avenue.
2019 ALUMNI KEYNOTE SPEAKER

BENJAMIN YOUNG, MD, PhD

Dr. Benjamin Young, MSTP Class of 1992, received his PhD in the Chemistry and Biochemistry department at Boulder with Dr. Thomas Cech and then completed residency in Internal Medicine and a fellowship in Infectious Disease both at the University of Colorado. Since then he has held a number of leadership positions and has continued to pursue clinical research in HIV. Among his numerous honors he has been awarded “Denver's Top Doctors” by 5280 magazine as well as “Outstanding HIV/AIDS Clinician and HIV Leadership Award” from TheBody.com a group dedicated to improving care and quality of life for those with HIV. Dr. Young educates physicians on HIV medicine worldwide, with experiences in Russia, Ukraine, Uzbekistan and The Netherlands. Currently Dr. Young is the Senior Global Medical Director for ViiV Healthcare, a group dedicated to innovative approaches to the challenges of HIV.

Need an icebreaker? Dr Young says to ask him about: medical sciences, public policy and human rights!
Dr. Anne Libby is the Vice Chair for Academic Affairs and Professor in the University of Colorado Department of Emergency Medicine. Dr. Libby’s research training includes a Ph.D. at Washington University in St. Louis Department of Economics and a postdoctoral fellowship at the University of California-Berkeley School of Public Health. Since joining CU’s Anschutz Medical Campus in 2000, she continues to build her local and national reputation focusing on the organization and financing of health care systems with a special emphasis on underserved populations and behavioral health. Dr. Libby is an expert on mentored research and leadership training. She has co-founded flagship faculty development training programs in the Colorado Clinical Translational Sciences Institute. Together with Judy Regensteiner, PhD, she co-directs the Doris Duke Charitable Foundation Fund to Retain Clinical Scientists and the Women’s Leadership Training Program, and is senior faculty at the Center for Women’s Health Research. She is a Gallup-Certified Strengths Coach and an inducted member of the Academy of Medical Educators.

Need an icebreaker? Dr Libby says to ask her about: Networking, negotiating for your career, mentorship, or women in medicine and science
**Student Oral Presentations**

**Session One**

**Megan Chriswell**, GS1, Khun lab
**Immunology**

**Cross-reactivity between autoantibodies and mucosal bacteria in pre-clinical rheumatoid arthritis: evidence of molecular mimicry driving disease initiation?**


Natural history studies in Rheumatoid Arthritis (RA) reveal the presence of a pre-disease “at-risk” state in first-degree relatives (FDRs) of RA probands characterized by antibodies to citrullinated protein antigens (ACPA). At-risk subjects have expanded circulating IgA+ plasmablasts as well as serum ACPA of the IgA isotype, suggesting a mucosal trigger for autoantibodies. We find that at-risk subjects have increased ACPA IgA in the feces as compared to healthy controls, further strengthening the connection between preclinical RA and the gut. Additionally, we evaluated the IgA-coated bacteria in feces of at-risk subjects by 16S sequencing of flow sorted IgA+ bacteria. At-risk subjects with fecal APCA IgA had increased IgA coating of Lachnospiraceae compared to fecal ACPA negative at-risk subjects. Next, we profiled cloned plasmablast monoclonal antibodies (mAbs) from at-risk subjects (n=94) and tested their reactivity against self and mucosal bacterial antigens. In addition to ACPA targets, 47% (n=44) of these mAbs were found to bind fecal bacteria, suggesting ACPA cross-reactivity. 16S sequencing of the mAb bound bacteria revealed preferential binding of Lachnospiraceae. Thus, through two independent methods, we identify a connection between mucosal ACPA and antibody reactivity to Lachnospiraceae that may be cross-reactive. These data suggest a mechanistic role for mucosal bacteria in the development of ACPA, and may help to better characterize the preclinical stage of RA.
Understanding the mechanism of bone marrow stromal cell-mediated protection of FLT3-ITD AML from FLT3-targeted therapy
Harry Park*, Mark Gregory, Vadym Zaberezhnyy, and James DeGregori

Internal tandem duplication (ITD) mutations in FMS-like tyrosine kinase 3 (FLT3) are among the most common mutations in AML and are particularly associated with a poor prognosis. FLT3-ITD causes constitutive activation of FLT3, leading to leukemogenesis. In clinical studies, patients treated with AC220, the most potent FLT3 inhibitor, demonstrated much more effective clearing of peripheral blasts than bone marrow blasts, implicating that bone marrow components may mediate drug resistance. Our lab has shown that FLT3 inhibition by AC220 impairs glutathione (GSH) metabolism and induces mitochondrial reactive oxygen species (mitoROS) accumulation in FLT3-ITD AML cells, which causes apoptotic cell death. However, whether and how these metabolic alterations influence bone marrow stromal cell-mediated protection of FLT3-ITD AML cells from AC220 treatment is not understood. My data suggest that when FLT3-ITD AML cells are treated with AC220 in conditioned media of bone marrow stromal cells, they fail to induce mitoROS and are protected from the killing effect of AC220. Interestingly, knockdown of ATM or G6PD in combination with AC220 substantially reverses the protection from mitoROS induction and subsequent cell death mediated by conditioned media. Furthermore, knockdown of ATM or G6PD results in significant reduction of mRNA levels of c-MYC and its target glutamine transporters in cells treated with AC220 in the presence of conditioned media. Given that glutamine is a key amino acid for GSH synthesis, my project attempts to understand how ATM and G6PD mediate bone marrow stromal cell protection, focusing on glutamine uptake and GSH metabolism. Findings from this research will provide new insights into the mechanism of bone marrow stromal cell-mediated protection of FLT3-ITD AML from FLT3-targeted therapy, and potentially identify additional targets for combinatorial therapies designed to overcome the protective effects of bone marrow stromal cells.
A Novel Human IL2RB Mutation Results in T and NK cell-driven Immune Dysregulation


The pleiotropic actions of interleukin-2 (IL-2) are essential for regulation of immune responses and maintenance of immune tolerance. The IL-2 receptor (IL-2R) is composed of IL-2Ra, IL-2Rb, and IL-2Rg subunits, with defects in IL-2Ra and IL-2Rg and their downstream signaling effectors resulting in known primary immunodeficiency disorders. Here, we report the first human defect in IL-2Rb, occurring in two infant siblings with a homozygous IL2RB mutation in the WSXWS motif, manifesting as multi-system autoimmunity and susceptibility to cytomegalovirus (CMV) infection. This mutation results in diminished IL-2Rb surface expression and impaired IL-2/15 signaling in CD8+ and CD4+ T cells, but not in NK cells. This hypomorphic mutation also leads to an increase in serum IL-2 and IL-15 levels but no other proinflammatory cytokines. Like IL-2Rb-/- mouse models, IL-2Rβ deficient patients demonstrated decreased Treg frequency, and lymphocytic infiltration into multiple tissues. In contrast to IL-2Rb-/- mice, who have a dramatic reduction in NK cells, both siblings demonstrated an expansion of NK cells with the accumulation of the immature CD56bright NK cell subset. This arrest in NK cell maturation results in the absence of a highly differentiated adaptive NK cell subpopulation, a subset implicated in immunity to CMV. Thus, we describe IL-2Rb deficiency as a novel primary immunodeficiency disease with prominent early-onset autoimmunity and immunodysregulation that are linked to functional deficits arising from altered IL-2Rb signaling in T and NK cells.
Long-term storage of memories in the central nervous system depends on the local dendritic synthesis and membrane trafficking of new synaptic proteins such as AMPA-type glutamate receptors (AMPAR). While traditional cell biology dictates that newly synthesized integral-membrane proteins require processing and sorting by the Golgi apparatus (GA) for trafficking, the GA is notably absent from most neuronal dendrites. Consequently, whether secretory cargoes are locally trafficked in dendrites, and if so, the identity and spatial organization of the organelles responsible for trafficking them remain unclear. We have utilized an inducible-ER release system in combination with live-cell fluorescence microscopy to define the dendritic organelles involved in trafficking new AMPA receptors. We found that upon exiting the dendritic endoplasmic reticulum (ER), AMPARs initially undergo spatially restricted entry into nearby ER-Golgi intermediate compartment (ERGIC) before accumulating in recycling endosomes (RE). Disrupting RE function drastically impairs the surface delivery of newly-released AMPARs, indicating that this pathway is critical for biosynthetic protein trafficking to the cell surface and individual synaptic sites. Surprisingly, RE-mediated surface delivery of AMPARs still occurred in the absence of normal GA function, indicating that locally translated proteins may be directly trafficked through this pathway without requiring processing by the somatic GA. Thus, in addition to its canonical role in recycling membrane proteins, the RE network also participates in a local, GA-independent trafficking pathway that could ultimately support translation-dependent forms of neural plasticity.
Impact of folding kinetics on the dimerization and dominance of tumor-derived p53 mutations
Ashley Denney*, Michael McMurray PhD

Protein folding in the crowded cytosolic environment is complex and, for many proteins, reliant on molecular chaperones to recognize aggregation-prone primary sequences and provide opportunities for proper folding. All cellular processes rely on the function of multi-subunit protein oligomers in which monomeric proteins interact stably with partner proteins. We are testing the hypothesis that prolonged interactions with chaperones can impose a disadvantage during oligomerization to slower-folding mutant proteins relative to their wild-type (WT) counterparts. We use two model oligomers to study this phenomenon: yeast septins and human p53. Septins are conserved eukaryotic GTP-binding proteins that serve essential cell division roles and p53 is a potent tumor suppressor widely mutated in cancer. Both derive function from higher-order oligomer assembly. We use a split-GFP approach in living yeast cells to identify and localize septin-chaperone and p53-chaperone interactions. Here we show that numerous cytosolic chaperones interact with WT septins, and that several Hsp70s, a chaperonin, and a disaggregase interact with mutant p53(V272M) but not WT p53. The functional impact of over-expression of candidate chaperones on mutant p53 is assessed using a transcriptional reporter, demonstrating that mutant p53(V272M) is functionally impeded by high levels of these chaperones. Finally, in an effort to understand which chaperones are functionally important for septin folding and oligomer assembly, we express and purify septins in chaperone-deleted bacteria and show oligomer defects in cells lacking the Hsp40 DnaJ or the Hsp70 DnaK. Folding-impaired proteins are thus more susceptible to kinetic trapping by chaperones during de novo synthesis and assembly, and chaperones may be important targets for diseases involving septin or p53 misfolding.
Uncovering spectral biomarkers of brain state

Elijah Christensen*, Aviva Abosch, John A. Thompson, Joel Zylberberg

Implantable neurostimulation devices are being used to treat a growing number of motor, psychiatric, and epileptic neurological disorders. Most of these devices are non-adaptive or “open-loop”, delivering constant stimulation without regard to underlying brain activity. In contrast, adaptive or “closed-loop” devices utilize real-time information on brain activity to deliver targeted stimulation on demand. Inference models capable of predicting brain states from the already implanted electrodes would facilitate closed-loop neurostimulation without additional hardware or surgeries. As a proof of concept, we developed a novel artificial neural network (ANN) that uses local field potentials (LFP) recorded from neurons in subthalamic nucleus (STN) to infer sleep stage in patients with Parkinson’s disease (PD). STN LFP recordings were collected from 9 PD patients, via a percutaneous cable attached to the implanted DBS electrode, during a full night’s sleep (6-8 hours) with concurrent polysomnography (PSG). We trained an ANN to prospectively identify sleep stage with PSG-level accuracy from 30-second epochs of LFP recordings. Our model’s sleep stage predictions match clinician-identified sleep stage with a mean accuracy of 91% on held-out epochs. Furthermore, Leave-One-Group-Out analysis also demonstrates 91% mean classification accuracy for novel subjects. These results, which classify sleep stage across a typical heterogeneous sample of PD patients, indicate spectral biomarkers present in LFP activity that can infer real-time brain states in PD patients with implanted DBS devices. Finally, these spectral signatures are not patient specific and likely generalize across the patient population. We intend to extend these preliminary results to other disease groups and brain activity patterns. Further development of this model may also focus on adapting stimulation during specific sleep stages to treat targeted sleep deficits.
Maternal western-style diet persistently alters bone and liver myeloid cell development and function in a non-human primate model

*Michael J. Nash, Taylor K. Soderborg, Rachel C. Janssen, Eric M. Pietras, Stephanie R. Wesolowski, Jacob E. Friedman

Poor maternal diet and obesity predisposes offspring to metabolic diseases such as obesity and non-alcoholic fatty liver disease (NAFLD). Macrophage dysfunction is a key aspect of obesity and NAFLD. During development macrophages arise from hematopoietic stem cells (HSC) that develop first in the liver before migrating to the bone marrow during late gestation. To investigate the impact of maternal western-style diet (MWSD) on development of HSC and macrophage function, we examined early third trimester fetuses and 3-year-old (3yo) offspring from MWSD mothers. 3yo offspring were maintained with MWSD mothers until weaning and then switched to a chow diet for the remaining 2.5 years. Colony-forming assays of plated fetal bone marrow cells showed a significant 34.5% relative increase in myeloid cells at the expense of erythroid (-78.9%) and multilineage (-53.8%) progenitors, and a decrease in total numbers of all cell colony types. Liver and bone marrow derived macrophages from fetuses exposed to MWSD were treated with LPS and showed significantly lower IL1B cytokine expression, suggesting decreased response to inflammatory stimuli. LPS induced cytokine expression was largely unchanged in 3yo bone marrow derived macrophage compared to controls, whereas in liver macrophage, IL-10 and TNF-a expression were increased. We also find increased periportal fibrosis histologically in livers from 3yo offspring, which implies macrophages may contribute to pathological fibrotic activity in the liver, driven by MWSD. Our ongoing studies are addressing whether MWSD impacts transcriptional pathways in HSCs related to mitochondrial metabolism, inflammatory immune response, and lymphoid to myeloid skewing. Overall our findings suggest that exposure to maternal WSD has long-term effects on HSC and macrophage function which may not resolve despite dietary intervention later in life, and which may play an important role in inflammation and fibrosis, characteristic of NAFLD.
Determinants of career outcomes of MSTP students at the University of Colorado (1985-2015)
Hannah A Scarborough*, Elizabeth Bowen, Arthur Gutierrez-Hartmann

MD-PhD programs were designed as an integrated approach to training physician-scientists, with the expectation that most graduates would be employed by academic medical centers or research institutes upon the completion of their residencies and fellowships. The University of Colorado began formally training physician scientists in 1981 and has received NIH/NIGMS support through an institutional grant since 1985. The MSTP provides full tuition and stipend support to its trainees and represents a large investment of institutional and federal resources. To date, there have been no studies correlating identifiable factors on an MSTP application or performance during medical/graduate school to career outcomes.

The purpose of this study is to identify determinants of eventual career outcomes of MSTP students at the University of Colorado. To this end, we have performed an analysis of MSTP trainees via publicly available data. The primary outcome measure is a category-based characterization, identifying whether a graduate is employed by an academic institution, in biotech/pharma/government, or in private practice. Secondary outcome measures include history of grant funding and post-graduation publication record.

We identified a number of factors that positively correlate with career retention in academia. These include publication during matriculation, female gender, and shorter length of residency. There was no identifiable correlation with time-to-graduation, receipt of an individual training grant as a pre-doctoral student, or specific specialty choice. The larger goal of this project is to study the relationship between performance and decisions of trainees as students to their eventual career decisions. We hope that a more thorough understanding of the factors that influence career outcomes can inform both the admissions and advising process of the University of Colorado MSTP.
## Poster Presentations

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17 Dylan Calame  Purkinje Cell Encoding of Limb Position in Skilled Reach
18 Eric Nguyen  Global profiling of hnRNP A2/B1-RNA binding on chromatin highlights IncRNA interactions
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22 Jon Kibbie  Butyrate differentially alters gut mucosal CD4 T cell activation and HIV-1 infection in vitro in a concentration dependent manner.
23 Karina Gomez  CD44 modulates cancer stem cell and macrophage interactions in head and neck cancer progression via stemness to invasion switch.
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Excellence in Service Award

This award aims to recognize an outstanding student in the University of Colorado MSTP that improves the lives of their fellow classmates and the experience of the MD/PhD training through their actions. Whether this person serves in an official role (eg: admissions, second look, curriculum committees) or takes initiative in an unofficial capacity (hosts dinners, brings people together across program years), his or her efforts are an example of self-less service. Please provide concrete examples of how the nominee serves the MSTP community.
Student Council Highlights: 2018-2019

**Student Council Mission:**
*Student Council, established in 2018, serves as a forum for MSTP students to connect with their program and their fellow classmates throughout their tenure at University of Colorado. Run by students, for the students, this council aims to unite the program from Anatomy Lab through Match Day. Student Council aims to facilitate the sharing of knowledge accumulated by students throughout their training and to develop a strong united voice.*

**Spotlight: Upcoming MSTP SC Events**

**Vote for the new UC MSTP logo!**
We’re getting a new logo! Keep an eye out for an opportunity to vote on your favorite design. Shout out to Jacqueline Turner & Bruce Kirkpatrick for spearheading this effort

**Revisit Weekend** - March 8-10th, 2019
Offers have been sent to our CU MSTP Class of 2019 recruits! Come get to know your future classmates and represent our program at great events all weekend. For more information, stay tuned for Student Council Emails or to get involved, ask Daniel Youmans.

**Advice: Applying For Residency** – April 25th, 2019 5:00-7:00pm Led by Eric Nguyen

**Student Council Elections** – May
Stay tuned for important information on running for student council positions and voting for next year’s leadership.

**Coffee Hour** – Every 2nd Monday 1:30-2:30pm
Come discuss MSTP related topics and/or to enjoy coffee, tea, and bagels with your fellow students.

**Other Important MSTP Related Events:**

**Match Day** - Friday, March, 15th, 2019

**34th Annual MD PhD Student Conference at Copper Mountain** - July 12-14th, 2019
Planned by CU MSTP Class of 2016
**Shout-outs: Past MSTP SC events**

The newly formed Student Council has been busy! Thanks to the hard work of our students with support from MSTP leadership, we’ve hosted several successful events geared toward improving the MSTP Student experience. Thank you to everyone who participated and special thanks to all who were directly involved in planning and helping make these events happen!

**MSTP P-day BBQ:** Led by Matt Becker and Taylor Soderborg  
**Choosing a lab:** Led by Jason Silver  
**Step 1 Advice:** Led by Roy Khair  
**Success in Clinic / Return to MS3:** Led by Joshua Wheeler  
**Monthly Coffee Hours:** Led by Student Council Leadership

**Annual MSTP Student Council Events:**

Your Student Council is working to establish an annual calendar of events to build a support structure/community for our program! Our goal is to provide support for students during key points in the program and comradery throughout the year. If you’re interested in getting involved or have an idea for an event, talk to one of your class reps, come to a coffee hour, or contact student council at mstpstudentcouncil@ucdenver.edu

**MSTP SC 2018-2019 Calendar of Events**

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<td>Applying to residency/step2</td>
<td>Q4</td>
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<td>May</td>
<td>Student council elections</td>
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<td>Graduation</td>
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<td>Un-Graduation</td>
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<td>Jul</td>
<td>MSTP P-day/BBQ</td>
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<td>National Student Conference</td>
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Thank you to all of our Student Council Members:

**Class Representatives:**

**Class of 2018**
- Thomas Forman
- William Sheeran
- Jacqueline Turner

**Class of 2017**
- Roy Khair
- Frances Li
- Lily Nguyen

**Class of 2016**
- Connor Hughes
- Taylor Yamauchi

**Class of 2015**
- Sarah Zych

**Class of 2014**
- Elijah Christensen
- Bob Jones
- Daniel Youmans

**Class of 2013**
- Devin Boe
- Alison Hixon
- Jon Kibbie
- Jason Silver

**Class of 2012**
- Joshua Wheeler

**Class of 2011**
- Eric Nguyen

**Class of 2010**
- Aaron Bowen
- Hannah Scarborough

**Class of 2009**
- Alexandra Antonioli

**Class of 2008**
- Hans Anderson

**Co-Presidents:**
- Taylor Soderborg
- Matt Becker
MSTP Curriculum Reform Committee:

The MSTP Student Council would like to recognize and thank the following students and faculty who are working hard to represent MSTP concerns and perspectives as the new Medical School Curriculum is formed.

Students:
- Juan Santiago-Moreno  MS1
- Will Sheeran  MS1
- Hei-Yong Lo  MS2
- Laurel Darragh  MS2
- Brian Lloyd  MS2
- Christopher Alderman  MS2
- Soraya Shehata  MS2
- Roy Khair  MS2
- Brigit-Alexandra High, GS1

- Austin Jolly  GS1
- Wells Lariviere  GS2
- Ruth Wang  GS3
- Mindy Szeto  GS3
- Philip Tatman  GS3
- Sarah Nelson  MS4
- Sarah Haeger  MS3
- Hans Anderson, MS2

Faculty:
- Patricia Ernst
- Arthur Gutierrez-Hartmann

- Chad Stickrath
- Liz Bowen
MSTP Student Council Retreat Planning Committee

Brigit High, Taylor Soderborg, Lily Nguyen, Taylor Yamauchi, Alison Hixon
Announcements

Have ideas or suggestions for the next retreat? How we can improve? What should we add to the schedule next year?

**Fill out for the post-retreat survey**

Coming to your inbox soon!

Acknowledgements

Thank you to Liz, Arthur, Jorge and Patricia for supporting the creation of this retreat and all the endeavors of the MSTP students

Thank you to the MSTP students for their participation in student council and this retreat

Thank you to faculty mentors, administration and alumni for their continued support of the MSTP
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