Melanoma Research Program

Congressionally Directed Medical Research Programs

CDMRP
Department of Defense

U.S. Army Medical Research
and Development Command

HISTORY

The Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 when, following a powerful grassroots effort led by the breast cancer advocacy community, Congress first appropriated funds to the Department of Defense (DoD) for biomedical research. The CDMRP has evolved into a global funding organization that fosters novel approaches to biomedical research in response to the needs of the American public, the military, and Congress. CDMRP funds are added annually to the DoD budget to support individual programs and are allocated via specific guidance from Congress. Over the course of its history, the CDMRP has managed $15.9 billion in Congressional appropriations for military and defense health research programs. CDMRP supports the entire research spectrum from basic research to clinical research and trials.

Melanoma Research Program

VISION

Prevent melanoma initiation and progression

MISSION

Earlier intervention to enhance mission readiness for US military personnel and to diminish the disease burden on Service members, Veterans, and the American public

BACKGROUND

Melanoma and other skin cancers (MOSC) research was funded by the CDMRP from fiscal years 2009-2018 (FY09-FY18) through the Peer Reviewed Cancer Research Program (PRCRP). The PRCRP invested $52.5 million (M) in melanoma research, representing 17% of total research dollars invested among more than 20 topics. A broad range of different melanoma research disciplines from detection and diagnosis to treatment has been funded (Figure 1). Throughout the years, the PRCRP invested in critical gaps in melanoma research and patient outcomes. Table 1 depicts some of the most promising of the PRCRP melanoma funded awards.

Figure 1: FY09-18 PRCRP Cancer Care Spectrum Investment for Melanoma Portfolio
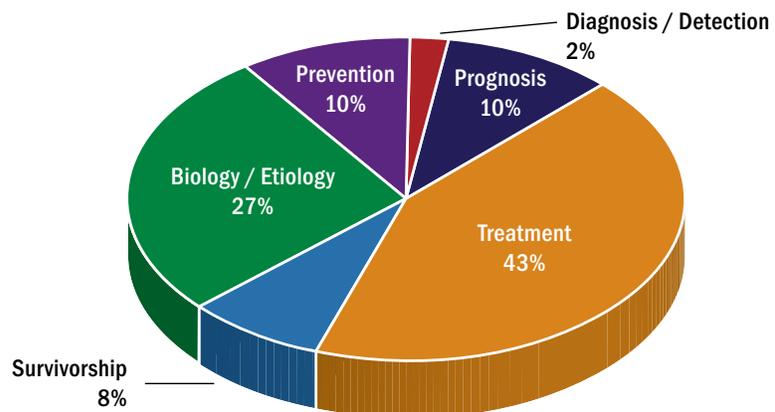
Melanoma is of particular interest to the U.S. military because active duty Service members spend prolonged periods outside, especially during deployment. Recent studies suggest that exposure to high levels of solar radiation in young adulthood is associated with a higher risk of melanoma mortality. According to the DoD Office of the Deputy Assistant Secretary of Defense for Military Community and Family Policy[1], 45% of the active duty force is 25 years or younger in age. A total of 92% of the active duty force is less than 40 years of age. In response, the U.S. Congress appropriated $10M to establish an individual stand-alone program, the Peer Reviewed Melanoma Research Program (MRP). In FY19, the MRP funded 15 applications, representing 18 awards. With the continuation of the MRP in FY20 with an appropriation of $20M.

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[1] https://download.militaryonesource.mil/12038/MOS/Reports/2018-demographics-report.pdf

THE MRP CHALLENGE STATEMENT

The MRP challenges the research community to redefine the concept of prevention. A new paradigm of prevention may include detecting, monitoring, and stopping the initiation of dysplasia; halting the progress to malignancy; blocking micro-metastases; or preventing emergence from tumor dormancy. The MRP challenges the research community to prevent melanoma earlier in the disease cycle, thus preventing metastasis. Prevention is viewed as the use of sunscreen/blockers to protect the melanocyte from harmful ultraviolet (UV) radiation. The MRP recognizes the usefulness of this strategy while tasking the research community to redefine prevention to include the entire melanomagenesis process. The MRP looks to shift the paradigm of prevention of all types of melanoma by investing in research studies focused on eliminating the progress of this deadly disease, whether it is cutaneous melanoma or a rare subtype.

Table 1: Toward Clinical Application of PRCRP-Funded Melanoma Awards

Fiscal Year	Principal Investigator(s)	Title and Main Conclusions/Outcomes
2009	Ruth Halaban, Ph.D., Douglas Brash, Ph.D.; Yale University	**UVL, ROS, Pigmentation, Genetic Predisposition, and Epigenetic Gene Silencing in Melanoma** This project led to the surprising discovery that UV-induced reactive oxygen and nitrogen species can generate cyclobutane pyrimidine dimers – the major mutagenic UV DNA photoproduct – in the dark for hours after sunlight exposure ends. The free radicals from UV-activated enzymes combine to excite an electron in melanin to a high energy that transfers to nearby DNA. These findings imply that melanin is hazardous as well as protective and suggest approaches to after-sun protection. *Four publications, one accompanied by a Perspectives article and 44 news reports.*
2014	J. William Harbour, M.D.; University of Miami, Coral Gables	**Development of Targeted Molecular Therapy for Cancers Harboring BAP1 Mutations** This project developed a novel high-throughput screening assay to identify compounds for treating cancers with BAP1 mutations, such as uveal melanoma and mesothelioma. Dr. Harbour identified an HDAC inhibitor, quisinostat, that rescues the BAP1-deficient phenotype. In BAP1-deficient uveal melanoma mouse models, quisinostat results in anti-proliferative and anti-tumorigenic properties. These results will inform the development of clinical trials for patients with BAP1-mutant cancers. *Two publications*
2014	Maureen Su, M.D.; University of North Carolina at Chapel Hill	**Central Tolerance Blockade to Augment Checkpoint Immunotherapy in Melanoma** Developed anti-RANKL antibody to block central tolerance and enhance the effect of immunological checkpoint inhibitors. A Phase II clinical trial in Stage III/IV melanoma patients has been initiated to study the antitumor effects of denosumab (anti-RANKL) in combination with pembrolizumab *Two publications*
2017	Yana Najjar, M.D. Greg Delgoffe, Ph.D.; University of Pittsburgh	**Metabolic Remodeling of the Tumor Microenvironment to Improve the Efficacy of Immunotherapy** Dr. Najjar is utilizing samples from a clinical trial examining the effect of anti-PD1 therapy in combination with the type-2 diabetes drug metformin in melanoma patients. Immune cell characteristics will be analyzed to demonstrate whether the addition of metformin improves the activity of anti-tumor immune cells. Preliminary evidence suggests that anti-PD1 and metformin modulates the phenotype of tumor-infiltrating lymphocytes that enter the tumor microenvironment.
2017	Ze'ev Ronai, Ph.D.; Sanford Burnham Presbys Medical Discovery Institute, La Jolla, CA.	**Siah2 Ubiquitin Ligase in Immune Checkpoint and Melanomagenesis** This project aims to characterize the role of Siah2, a ubiquitin ligase, in regulating the immune response to melanoma. Dr. Ronai demonstrated that Siah2 regulates Treg recruitment and cell cycle progression, thereby controlling melanoma development. Loss of Siah2 sensitizes melanoma to immune checkpoint blockade therapy, representing a potential new avenue for drug development.
2014/2018	Khalid Shah, Ph.D., David Fisher, M.D., Ph.D.; Massachusetts General Hospital, Brigham and Women's Hospital	**Stem Cell-Loaded Oncolytic Viruses for Metastatic Melanomas** Dr. Shah and his team have shown that engineered mesenchymal stem cells (MSC) home to melanoma tumor sites in the brain and release oncolytic herpes virus (oHSV) at the site of the tumors. The project aims to evaluate the fate and therapeutic efficacy of MSC-oHSV and gene-edited MSC releasing immunomodulators in metastatic melanoma tumor models. These studies will present a major step forward in the use of oncolytic viruses in brain metastatic melanomas. Future clinical trials are planned. *One publication, multiple news releases.*

Highlights of FY19 MRP Awards
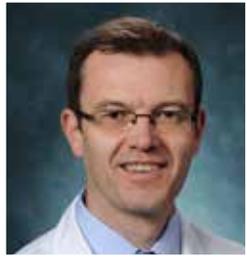
The Kinome of GNAQ/11-Mutant Uveal Melanoma

Andrew Aplin, Ph.D., Thomas Jefferson University
FY19 Idea Award

Uveal melanoma is a rare form of cancer that develops from melanocytes in the eye. Although it is a rare cancer, it is the most common ocular malignancy in adults. Metastasis occurs, most commonly to the liver; once the disease has spread, the 5-year survival rate is less than 15%. There is an urgent need to develop effective treatments for metastatic uveal melanoma.

Dr. Aplin's FY19 Idea Award aims to identify kinases regulated by the protein products of the genes, GNAQ and GNA11, which are the most commonly mutated genes in uveal melanoma. GNAQ and GNA11 play roles in intracellular signaling pathways. The mutations observed in uveal melanoma lead to constitutive activation of GNAQ and GNA11, which in turn can lead to dysregulation of signaling pathways and thus aberrant cell growth and proliferation. Dr. Aplin's team will explore how the tumor suppressor BAP1 plays a role in these critical kinase signaling pathways. Loss of BAP1 in uveal melanocytes results in a de-differentiated state, in which the cells lose melanocyte characteristics and revert to a "stem cell-like" phenotype. It is unknown how loss of BAP1 and the de-differentiated phenotype contributes to metastatic progression. In order to identify the kinases regulated by these crucial pathways, Dr. Aplin will collaborate with Dr. James Duncan (Fox Chase Cancer Center), who developed a new proteomic kinase profiling method to uncover novel signaling networks. The most promising candidate kinases will be further investigated to determine their biological function in regulating the proliferation of uveal melanoma cells. These studies are expected to pinpoint protein kinases that are regulated by mutant GNAQ, GNA11, and BAP1. Dr. Aplin anticipates that these kinases will represent potential therapeutic targets for the treatment of metastatic uveal melanoma. Ultimately, conclusions from this project will hopefully lead to clinical studies and address a major gap in the treatment of rare melanomas that affect Service members, Veterans, and the American public.

Immune Profiling of Sentinel Lymph Nodes in Melanoma

Mark Faries, M.D., Cedars-Sinai Medical Center
FY19 Translational Research Award

The sentinel lymph node (SLN) is a critical site in tumor-immune interactions in melanoma. Biopsy of the SLN is a standard component of melanoma treatment that provides critical disease-staging information and is often a determinant of adjuvant therapies and follow-up treatment regimens. While the SLN is the most common site of initial metastasis, melanoma progression patterns from the SLN have major implications in therapy selection and vary from patient to patient. With funding from an FY19 Translational Research Award, Dr. Mark Faries will examine the immune microenvironment of SLNs in clinically distinct cohorts of melanoma patients to determine whether immune-melanoma interactions in the SLN can define the course of a patient's disease progression and predict treatment response.

To identify SLNs, lymphatic mapping procedures that utilize vital blue dye and a radio-colloid tracer are used during surgery. Low colloid uptake by the SLN is associated with poor survival, increased in-transit and distant metastasis, and decreased nodal metastasis. Previous work performed by Dr. Faries has shown that uptake of the colloid tracer in SLNs is immune-based and declines with age. Within the SLN, there appears to be a loss of dendritic cell area and dendritic networks, which may compromise nodal immune function; however, the components and mechanisms of this immune suppression and dysfunction remain unknown. Using two histological imaging modalities, image mass cytometry and multiplex immunohistochemistry, Dr. Faries aims to identify and validate tumor-immune interaction features in the SLN and predict progression patterns and tumor responsiveness to therapy in clinically distinct cohorts. If successful, the results of this study could have a number of significant impacts on patient prognosis and treatment. Identification of the mechanisms underlying compromised immune function and inhibited uptake and retention of colloid tracers in SLNs could be used to prospectively evaluate current patients and may aid providers in assessing risk based on SLN findings. Additionally, by identifying the immune conditions in SLNs leading to distinct patterns of progression, clinicians may be able to select more appropriate therapies for their patients. Finally, identification of biomarkers in the SLNs of patients receiving checkpoint inhibitor medications that predict patient response will aid in identifying future patients who may benefit the most from checkpoint inhibitor therapy. Taken together, the results of this study could lead to identification and investigation of novel treatment strategies for melanoma progression to metastases.

Joann G. Elmore

Linda Shapiro

Improving the Diagnosis of Melanoma and Precursor Lesions Among Veterans: Developing Artificial Intelligence Techniques and Teledermatopathology

Joann G. Elmore, M.D., M.P.H., University of California Los Angeles
**Linda Shapiro, Ph.D., University of Washington**
FY19 Team Science Award

In recent decades, U.S. military members have been deployed to areas of high levels of solar radiation, thus potentially exposing active duty Service members to damaging UV light. Studies have suggested that UV exposures in young adulthood are associated with a higher risk of melanoma diagnoses. Melanoma cases are increasing among military members, with the greatest incidence rates in the Air Force, Navy, and the Marines. Within the U.S. Department of Veterans Affairs (VA) health system, a high volume of skin biopsies are obtained each year. It is estimated that 40% to 50% of specimens analyzed by pathologists in the VA health system are skin biopsies; however, most VA hospitals do not staff dermatopathologists (pathologists who specialize in interpreting skin biopsy specimens). The evaluation of suspicious skin lesions by pathologists is challenging and highly subjective. A pathologists' assessment of a skin biopsy specimen establishes whether a melanoma diagnosis is present or absent and guides physicians to select the appropriate treatment. An incorrect diagnosis by a pathologist leads to false negatives and/or false positives.

Prior work by Dr. Elmore's team at the University of California at Los Angeles demonstrated concerning low levels of diagnostic accuracy among pathologists interpreting skin biopsy specimens. For example, Figure 2 shows an example of a single melanoma in situ case, revealing marked disagreement among community pathologists who each independently interpreted the same specimen, with their diagnoses ranging from benign to invasive melanoma. It is estimated that about 16.8% of all diagnoses of skin lesions are incorrect in the U.S.[1] These findings highlight limitations in our current histologic diagnoses and highlight the need for new approaches. Lack of accurate and precise dermatological examination causes a heavy burden on the Veterans Health Administration.

Dr. Elmore's team, including co-investigator Dr. Linda Shapiro and Dr. Oliver Chang from the University of Washington, aims to understand dermatopathologists' viewing behaviors as well as the integration of Artificial Intelligence (AI)/machine learning to improve melanoma diagnosis methods. Dr. Chang, who is also a dermatopathologist at Puget Sound VA Hospital, will lead the effort to establish a VA dermatopathology consultation network and a digital catalog of specimens. Dermatopathologists' viewing behaviors as they read digital skin biopsy slides will be documented to support human-computer interface AI/machine learning tools. Finally, Drs. Elmore and Shapiro will use computer vision and machine learning techniques to study the associations of human viewing behaviors with identification of regions of interest to ultimately design classification models. The goal of the study includes a better understanding of human dermatopathologists' viewing behaviors and how it influences the diagnosis. This, in turn, will assist the team in the future design of human-centered AI/machine learning tools to supplement human-led diagnosis and improve diagnostic accuracy.

Figure 2: Slide of Skin Biopsy
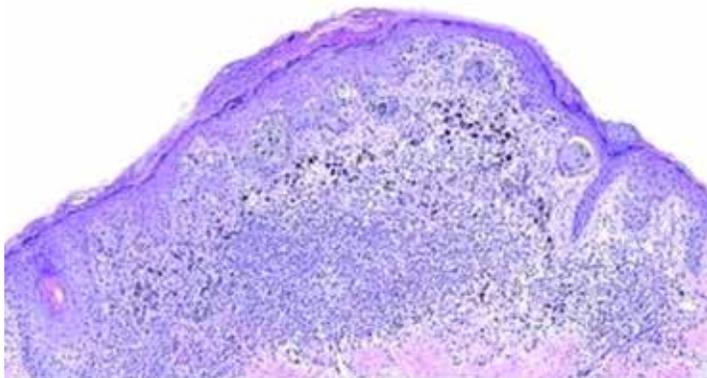
This skin biopsy glass slide was determined by our expert consensus panel to be melanoma in situ. This slide was independently diagnosed by 37 community pathologists in our prior work and diagnoses included:
- benign lesion requiring no further treatment (n=9)
- compound nevus (n=3)
- moderately dysplastic nevus (n=11)
- melanoma in situ/severely dysplastic nevus (n=7)
- melanocytic lesions of uncertain malignancy potential (n=2)
- invasive melanoma stage T1a (n=1)
- invasive melanoma stage T1b (n=4)

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[1] Elmore JG, Barnhill RL, Elder DE, et al. 2017. Pathologists' Diagnosis of Invasive Melanoma and Melanocytic Proliferations: Observer Accuracy and Reproducibility Study. BMJ 357:j2813.

Mechanisms of UV-Induced Melanoma Initiation

Douglas Grossman, M.D., Ph.D., University of Utah
**Matthew VanBrocklin, Ph.D., University of Utah**
Robert Judson-Torres, Ph.D., University of Utah
FY19 Team Science Award

Exposure to UV radiation in sunlight is a major environmental risk factor for cutaneous melanoma. UV light induces pathogenic mutations, inflammation, and activates melanocyte signaling pathways. BRAF mutations drive the early stages of melanoma progression in 60% of cases, suggesting that inflammation and activation of melanocyte signaling pathways are also potential drivers of melanomagenesis. Dr. Grossman and his colleagues, Dr. VanBrocklin and Dr. Judson-Torres, have preliminary data demonstrating that UV-induced inflammation and G-protein-coupled receptor (GPCR) signaling, a pathway that plays a crucial role in melanocyte development, proliferation, and differentiation, results in the initiation of melanoma by inducing bi-directional interconversion between tumor-initiating and non-tumor-initiating melanocytes. With funding from an FY19 Team Science Award, Drs. Grossman, VanBrocklin, and Judson-Torres bring together their expertise in basic, translational, and clinical research to assess the impact of UV-induced inflammatory and GPCR signaling on causing melanoma initiation.

The findings of this study may have significant impact on melanoma prevention strategies, which rely heavily on limiting UV exposure or identifying melanomas soon after they form. If the current study is successful, it will provide evidence that alterations in inflammatory and GPCR signaling following UV exposure—not DNA damage—are primarily responsible for melanoma initiation (Figure 3). This finding would support the use of novel prevention strategies, such as the use of compounds that regulate the inflammatory and GPCR signaling pathways that are already approved for clinical use. Additionally, small molecules that interrupt these pathways could be used in conjunction with traditional UV exposure prevention methods as another mechanism of protection against melanoma initiation. The study designed by Drs. Grossman, VanBrocklin, and Judson-Torres takes a fundamentally different approach to melanoma prevention and could lead to novel strategies that prevent melanoma even after UV exposure.

Douglas Grossman

Matthew VanBrocklin

Robert Judson-Torres

Figure 3: Prevention, Initiation, and Detection of Melanoma
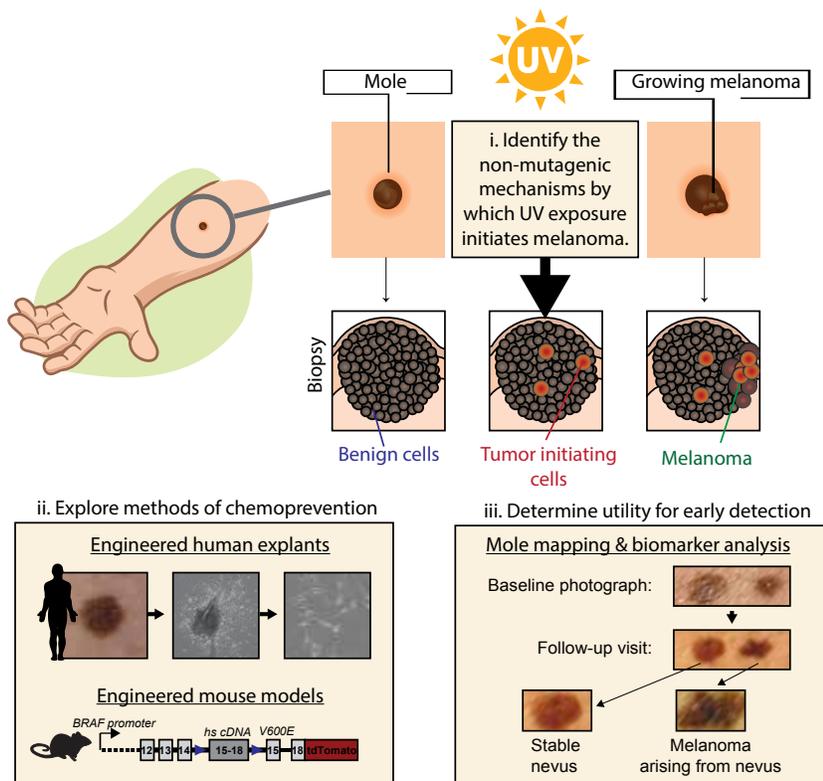
Targeting Acral Melanoma by Inducing TERT Degradation

Jessie Villanueva, Ph.D., The Wistar Institute
FY19 Idea Award

Acral lentiginous melanoma (ALM) is a subtype of melanoma that develops on the palms, soles, or nail beds. ALM is the most common type of melanoma that occurs in people with darker skin and those of Asian descent. This sub-type of melanoma is usually diagnosed in later stages of the disease, when it is more difficult to treat. There are currently no effective pharmaceutical treatments for ALM.

With funding from an FY19 MRP Idea Award, Dr. Villanueava will target the telomerase reverse transcriptase (TERT) subunit. The role of telomerase is to extend and protect the ends of chromosomes, which are called telomeres. In most normal healthy cells, TERT is not expressed, and telomeres shorten each time a cell divides. When the telomeres become too short, the cell will initiate programmed cell death. In most cancers, TERT is reactivated, protecting the telomeres and allowing the cells to become immortal, which facilitates the development of tumors.

TERT alterations are present in over 40% of ALM cases. Therefore, TERT is an attractive therapeutic target for ALM, as blocking TERT function would mainly impact cancer cells instead of healthy cells. Dr. Villanueva hypothesizes that pharmacological strategies inducing degradation of TERT will trigger death of ALM cells. The first part of the project is to develop molecules that selectively bind to TERT and induce its degradation. The most promising compounds developed will then be tested in ALM patient-derived organoids in vitro and patient-derived xenografts in vivo. By developing an effective approach for therapeutic targeting of TERT, Dr. Villanueva's project opens new avenues to improve the treatment outcomes and quality of life of ALM patients.

Consumer Highlight

A Surprise Diagnosis, a Community, and a Chance to Make a Difference in Melanoma Patients' Lives

JB Ward

I was mom to a healthy 1-year-old, preparing to return some of my focus back to the psychology degree sitting on my shelf, when I got the most shocking news of my life. I was diagnosed with a rare and very aggressive form of melanoma (vaginal mucosal melanoma), with no known cause or predisposing factors and almost no chance of effective treatment. In the year that followed, I experienced more fear, disappointment, and frustration than ever before in my life, yet I also found myself experiencing what seemed to be miracles of timing, perseverance, and advancing medical science.

It's difficult to believe that I received that news over 4 years ago and that I was given just a 5% chance of surviving. Today, I am healthy, with no reoccurrence in over 3 years. After being granted this second chance at life, in no small part due to the innovative and improving therapies coming from the dedicated medical science community, I can hardly keep myself away from any opportunity to give back in the hopes that others can be granted a second chance too.

I have been involved with more than one of the melanoma support foundations and communities, including the Melanoma Research Foundation, the AIM at Melanoma Foundation (AIM), and an in-progress, patient advocate-driven research initiative for mucosal melanoma in partnership with the Melanoma Research Alliance. These organizations are dedicated to improving outcomes and quality-of-life for people impacted by a malignant melanoma diagnosis. It was through AIM, after involvement with a couple of other advocacy opportunities with them, that I was nominated to apply to be a consumer reviewer for peer review with the new MRP with the CDMRP.

The entire process with the CDMRP, from application to completion, has been positive, supportive, and one of the most intrinsically rewarding experiences I have ever been involved with. I felt that I was approached as a human first, panel member second, and all I had to do to make the greatest impact was to show up as myself – just as I am. This tone and expectation set by the CDMRP was matched by the impressive community spirit brought by the expert panelists; there was never a moment when I felt that my views, beliefs, and input were not considered just as valuable as those of the experts.

The work that the CDMRP is doing is changing lives and changing history. Their dedication to consumers and patient advocates is admirable and inspiring, and I look forward to many more opportunities to work with these wonderful people through this important program that supports the most promising research, granting someone else a second chance at life too.

For more information, please visit
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