

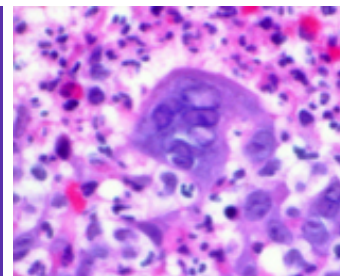


# eLITERATURE REVIEW

## eMedicalDermatology Review

Presented by  
The Johns Hopkins University  
School of Medicine & The Institute  
for Johns Hopkins Nursing

Supported by an Educational Grant  
from Centocor, Inc.



HOME CME/CNE INFORMATION PROGRAM DIRECTORS NEWSLETTER ARCHIVE EDIT PROFILE RECOMMEND TO A COLLEAGUE

### April 2009: VOLUME 1, NUMBER 12

#### *Melanoma Outcomes Among Solid Organ Transplant Recipients and Controversial Topics in Treatment*



#### In this Issue...

While melanoma outcomes in the general population have been well documented and vary significantly based on the stage of disease, little is known about the outcomes associated with malignant melanoma in immunosuppressed solid organ transplant recipients. These melanomas occur in 3 main clinical settings—(1) donor-derived melanoma, (2) melanoma preceding transplantation, and (3) de novo melanoma following solid organ transplantation—with the last group comprising the most common clinical scenario.

In this issue, we review recent articles that compare the outcomes of malignant melanoma in immunosuppressed solid organ transplant recipients with the general population, and that investigate the clinical thresholds for and the risks associated with reducing immunosuppression as a therapeutic strategy. In addition, as conversion from calcineurin inhibitor-based regimens to mammalian target of rapamycin (mTOR)-based regimens is becoming increasingly popular, we discuss the research into the potential immunosuppressant and antineoplastic properties of mTOR-based regimens.

#### Program Information

- [CE Info](#)
- [Accreditation](#)
- [Credit Designations](#)
- [Intended Audience](#)
- [Learning Objectives](#)
- [Internet CME/CNE Policy](#)
- [Faculty Disclosure](#)
- [Disclaimer Statement](#)

#### Length of Activity

- 1 hour Physicians
- 1 contact hour Nurses

#### Release Date

April 29, 2009

#### Expiration Date

April 28, 2011

#### COMPLETE THE POST-TEST

##### Step 1.

Click on the appropriate link below. This will take you to the post-test.

##### Step 2.

If you have participated in a Johns Hopkins on-line course, login. Otherwise, please register.

##### Step 3.

Complete the post-test and course evaluation.

##### Step 4.

Print out your certificate.

PHYSICIAN  
POST-TEST

NURSE  
POST-TEST

### LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Assess outcomes with stage T1 and T2 disease in patients with post-transplant melanoma
- Evaluate outcomes with stage T3 and T4 disease in patients with post-transplant melanoma
- Identify the post-transplantation risks associated with pre-transplant melanoma

#### IMPORTANT CME/CNE INFORMATION

▼ Program Begins Below

##### ACCREDITATION STATEMENTS

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

##### FACULTY DISCLOSURE

As a provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of Johns Hopkins University School of Medicine to require the disclosure of the existence of any significant financial interest or any other relationship a faculty member or a provider has with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. The Program Directors reported the following:

- **Bernard A. Cohen, MD**, has indicated a past and current financial relationship with Novartis, Pharmaceuticals, Astellas Pharma Inc., Medicis and Connetics. He served on the Speaker's

## CREDIT DESIGNATIONS

### Physicians

The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*<sup>™</sup>. Physicians should only claim credit commensurate with the extent of their participation in this activity.

### Nurses

This 1.0 contact hour Educational Activity is provided by The Institute for Johns Hopkins Nursing. Each Newsletter carries a maximum of 1 contact hours.

## POST-TEST

To take the post-test for eMedicalDermatology Review you will need to visit [The Johns Hopkins University School of Medicine's CME website](#) or [The Institute for Johns Hopkins Nursing](#). If you have already registered for another Hopkins CME program at these sites, simply enter the requested information when prompted. Otherwise, complete the registration form to begin the testing process. A passing grade of 70% or higher on the post test/evaluation is required to receive CME/CNE credit.

## STATEMENT OF RESPONSIBILITY

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality, and scientific integrity of this CME/CNE activity.

## INTENDED AUDIENCE

This activity has been developed for the Dermatologist, PharmD, Nurses, Dermasurgeon, Dermatopathologist, Pediatric Dermatologist, Immunodermatologist, and Wound Care Specialist.

## LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Assess outcomes with stage T1 and T2 disease in patients with post-transplant melanoma
- Evaluate outcomes with stage T3 and T4 disease in patients with post-transplant melanoma
- Identify the post-transplantation risks associated with pre-transplant melanoma

## LAUNCH DATE

April 29, 2009

Bureau for Novartis, Pharmaceuticals, Astellas Pharma Inc., and Medicis. He has also received grants for studies from Novartis, Pharmaceuticals and Astellas Pharma Inc. and received support for a fellowship program from Connetics.

- **Susan Matra Rabizadeh, MD, MBA** has disclosed no relationship with commercial supporters.
- **Mark Lebwohl, MD** has disclosed that he has received grants for clinical research and educational activities from, has served as an advisor, consultant and speaker to, and has served as an investigator for Abbott, Amgen, Astellas, Centocor, Genentech and Novartis.
- **Elizabeth Sloand, PhD, CRNP** has disclosed no relationships with commercial supporters.

## [Guest Author's Disclosures](#)

## INTERNET CME/CE POLICY

The Offices of Continuing Education (CE) at The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing are committed to protect the privacy of its members and customers. The Johns Hopkins University maintains its Internet site as an information resource and service for physicians, other health professionals and the public.

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing will keep your personal and credit information confidential when you participate in a CE Internet based program. Your information will never be given to anyone outside The Johns Hopkins University program. CE collects only the information necessary to provide you with the service you request.

## DISCLAIMER STATEMENT

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only. Use of Johns Hopkins University School of Medicine name implies review of educational format design and approach. Please review the complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings and adverse effects before administering pharmacologic therapy to patients.

## HARDWARE & SOFTWARE REQUIREMENTS

Pentium 800 processor or greater, Windows 98/NT/2000/XP or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, 56K Modem or better, Windows Media Player 9.0 or later, 128 MB of RAM  
Monitor settings: High color at 800 x 600 pixels, Sound card and speakers, Adobe Acrobat Reader.

## THIS ISSUE

- [COMMENTARY from our Guest Author](#)
- [CLINICOPATHOLOGIC FEATURES AND MELANOMA OUTCOMES AMONG ORGAN TRANSPLANT RECIPIENTS](#)
- [MELANOMA OUTCOMES AMONG SOLID ORGAN TRANSPLANT RECIPIENTS](#)
- [RISKS ASSOCIATED WITH REDUCTION OF IMMUNOSUPPRESSION IN PATIENTS WITH TRANSPLANT-ASSOCIATED SKIN CANCER](#)

## Program Directors

### **Bernard A. Cohen, MD**

Professor of Pediatrics and Dermatology and Director of Pediatric Dermatology,  
Johns Hopkins Children's Center  
Baltimore, MD

### **Susan Matra Rabizadeh, MD, MBA**

Private Practice  
Los Angeles, CA

### **Mark Lebwohl, MD**

Professor and Chairman  
Department of Dermatology  
The Mount Sinai School of Medicine  
New York, NY

■ [ACTIVATION OF mTOR IN PATIENTS WITH MALIGNANT MELANOMA](#)

**Elizabeth Sloand, PhD, CRNP**  
Assistant Professor of Pediatric Nursing  
The Johns Hopkins University  
School of Nursing  
Baltimore, MD

## GUEST AUTHOR OF THE MONTH



Commentary & Reviews:  
**Manisha J. Patel, MD**  
Assistant Professor,  
Department of Dermatology  
Johns Hopkins University  
School of Medicine  
Baltimore, Maryland

### ***Guest Faculty Disclosures***

**Dr. Patel** has disclosed no relationships with commercial supporters.

### ***Unlabeled/Unapproved Uses***

The authors have indicated that there will be no reference to unlabeled or unapproved uses of drugs or products in this presentation.

### [Program Directors' Disclosures](#)

## COMMENTARY

Melanoma is an aggressive cutaneous malignancy that accounts for only 4% of all skin cancers but is associated with 74% of all skin cancer–related deaths.<sup>1</sup> The incidence of malignant melanoma in the general population is on the rise, with estimated rates likely to triple over the next 30 years.<sup>2</sup> Studies have supported the strong influence of the immune system on the pathogenesis and progression of malignant melanoma. It has therefore been suggested that melanoma might develop more often in patients who are immunosuppressed and have worse outcomes. With improved long-term survival and older age at transplant, melanoma is, therefore, likely to become an increasingly significant problem in the context of organ transplantation.

The medical literature has raised considerable concern regarding poor outcomes in transplant recipients with melanoma; however, many of these reports lack current staging information, thus limiting their accurate interpretation and application to the current management of patients. In addition, the incidence of melanoma among transplant patients is debatable, with various reports citing a risk for occurrence that is 0 to 8 times higher than that in the general population (as noted by Dapprich and colleagues). There are additional variations in incidence dependent on the type of transplanted organ studied.

Current treatment of melanoma in organ transplant patients is similar to that in the nonimmunosuppressed population, although expanded options include reduction of immunosuppression and a switch from calcineurin inhibitor–based regimens to mTOR inhibitors. Additional studies designed to examine the effects of these treatment options are needed. Given the current lack of effective treatments for advanced malignant melanoma, regular skin surveillance with a view toward early curative surgical intervention is likely to have the greatest impact on mortality in the coming years. Evidence suggests that dedicated transplant dermatology clinics are the most effective means of achieving this goal.<sup>3</sup>

RECOMMEND TO  
A COLLEAGUE

NEWSLETTER  
ARCHIVE

## References

1. American Cancer Society. [Cancer Facts and Figures 2005](#). Atlanta, GA: American Cancer Society; 2005.
2. Diffey BL. [The future incidence of cutaneous melanoma within the UK](#) *Br J Dermatol*. 2004;151(4):868-872.
3. Ismail F, Mitchell L, Casabonne D, et al. [Specialist dermatology clinics for organ transplant recipients significantly improve compliance with photoprotection and levels of skin cancer awareness](#). *Br J Dermatol*. 2006;155(5):916-925.

## CLINICOPATHOLOGIC FEATURES AND MELANOMA OUTCOMES AMONG ORGAN TRANSPLANT RECIPIENTS

Matin RN, Mesher D, Proby CM, et al; Skin Care in Organ Transplant Patients, Europe (SCOPE) group. **Melanoma in organ transplant recipients: clinicopathological features and outcome in 100 cases**. *Am J Transplant*. 2008;(8)9: 1891-1900.

(For non-journal subscribers, an additional fee may apply for full text articles.)



[View journal abstract](#)



[View full article](#)

Although organ transplant recipients have a higher incidence of melanoma than the general population, the prognosis of this potentially fatal skin cancer in this group of patients has yet to be established. To address this issue, a multicenter, retrospective analysis was conducted to assess outcomes for 100 melanomas (91 post-transplant and 9 pre-transplant) in 95 individuals. Data were collected from 14 specialist transplant dermatology clinics across Europe, and were compared with age-, sex-, tumor thickness-, and ulceration status-matched controls from the American Joint Committee on Cancer (AJCC) melanoma database.

Outcomes for patients with stage T1 and T2 tumors, compared with corresponding AJCC control groups, did not differ significantly for T1 alone, or for combined stage T1 and T2 post-transplant melanomas. In this group, the hazard ratio (HR) was 1.45 (95% confidence interval [CI], 0.31 to 6.89), demonstrating a slightly increased, although nonsignificant, rate of death in the transplant patients. The prognosis was significantly worse among patients with post-transplant melanoma stage T3 ( $P=.0126$ ) and T4 ( $P=.0001$ ) disease. The outcome for combined T3 and T4 melanomas was also significantly worse ( $P<.0001$ ), with an HR of 11.49 (95% CI, 3.59 to 36.82). Among the 9 pre-transplant melanoma cases, no melanoma-related deaths were reported. The median interval between diagnosis and transplant was 7.8 years. Three melanomas were stage T1 at diagnosis. The mean post-transplant follow-up was 5 years.

Among patients with post-transplant cutaneous melanoma, 5-year survival for T1 and T2 disease ( $\leq 2$  mm thickness) was similar to that in the AJCC control population. However, prognosis was significantly worse in patients with post-transplant tumors of stage T3 or higher ( $P<.0001$ ). In all cases of post-transplant primary cutaneous melanoma, surgical wide local excision was the initial treatment. The study found no significant difference in mortality between the group in whom immunosuppression was reduced and those in whom it was not altered. However, the data on which this analysis was based were limited. Until information from larger studies becomes available, each case should be assessed on an individual basis, with guidance from a recent expert consensus opinion statement on this subject.<sup>1</sup>

This is the first study to stratify patients according to a number of AJCC prognostic criteria. Overall mortality in the post-transplant cutaneous melanoma cohort from all causes was 27% and melanoma-specific mortality was 13%. The data shows significantly more deaths among patients with T3 and T4 post-transplant tumors compared with the AJCC population ( $P<.0001$ ). Although this study demonstrates the reduced survival in those with T3 and T4 melanomas, additional research is needed to quantify more

 RECOMMEND TO  
A COLLEAGUE

 NEWSLETTER  
ARCHIVE

accurately this reduction in survival, as well as to confirm that survival in patients with T1 and T2 melanomas is unaffected by transplantation, given the small number of deaths in this group.

Neither this study nor prior investigations have provided an adequate evidence base for reliable recommendation of the interval postmelanoma for which transplantation could be considered risk-free. Such cases need to take into account the risks associated with delaying transplantation. With patients surviving longer and transplants occurring at a later age, melanoma is likely to emerge as an increasing clinical problem in this context. Regular skin surveillance with a view toward early curative surgical intervention is likely to have a significant impact on mortality in the coming years, with evidence suggesting that dedicated transplant dermatology clinics are the most effective way of attaining this goal.<sup>2</sup>

## References

1. Otley C, Berg D, Ulrich C, et al. Reduction of Immunosuppression Task Force of the International Transplant Skin Cancer Collaborative and the Skin Care in Organ Transplant Patients Europe. [Reduction of immunosuppression for transplant-associated skin cancer: expert consensus survey](#). *Br J Dermatol*. 2006;154(3):395-400.
2. Ismail F, Mitchell L, Casabonne D, et al. [Specialist dermatology clinics for organ transplant recipients significantly improve compliance with photoprotection and levels of skin cancer awareness](#). *Br J Dermatol*. 2006;155(5):916-925.

## MELANOMA OUTCOMES AMONG SOLID ORGAN TRANSPLANT RECIPIENTS

Dapprich D, Weenig R, Rohlinger A, et al. **Outcomes of melanoma in recipients of solid organ transplant**. *J Am Acad Dermatol*. 2008;59(3): 405-417.

(For non-journal subscribers, an additional fee may apply for full text articles.)



[View journal abstract](#)



[View full article](#)

Concern exists that the immunologic tumor malignant melanoma may have worse outcomes in immunosuppressed hosts than in the general population. This study sought to describe melanoma outcomes in immunosuppressed solid organ transplant recipients and to compare them with those in the general population. The researchers, from the Mayo Clinic in Rochester, Minnesota, conducted a retrospective review of medical charts and pathology slides from cases of melanoma and solid organ transplantation between 1978 and 2007, in order to compare patient outcomes.

A total of 48 melanomas were identified in 43 transplant recipients. None of the 12 patients with melanoma prior to transplant experienced a melanoma recurrence, subsequent metastasis, or death due to melanoma. Of the 31 patients with melanoma diagnosed following transplantation, 8 were known to have died of any cause at follow-up, but only 2 died of melanoma. Among these 31 patients, metastases developed in 3 individuals (stages IB, IIA, and IIIB), and 2 persons experienced disease recurrence (stages IA and IB).

Outcomes of melanoma among immunosuppressed transplant recipients appeared similar to those among prognostically matched nonimmunosuppressed hosts. However, the small number of cases limited statistical comparisons. Although this study does not statistically confirm or refute a worse prognosis, its trends differ from those of previous case reports and case series published in the medical literature, which had raised concerns over a worse prognosis.

The most notable limitation of this study is the number of patients and cases of melanoma, which were too small to allow meaningful statistical analysis and valid statistical comparisons. In addition, the limited number of events (ie, death caused by disease) prevented evaluation of the effect of various prognostic and risk factors on patient outcomes.

 RECOMMEND TO A COLLEAGUE

 NEWSLETTER ARCHIVE

## RISKS ASSOCIATED WITH REDUCTION OF IMMUNOSUPPRESSION IN PATIENTS WITH TRANSPLANT-ASSOCIATED SKIN CANCER

Otley CC, Griffin MD, Charlton MR, Edwards BS, Neuburg M, Stasko T; Reduction of Immunosuppression Task Force of the International Transplant Skin Cancer Collaborative. **Reduction of immunosuppression for transplant-associated skin cancer: thresholds and risks.** *Br J Dermatol.* 2007;157(6):1183-1188.

(For non-journal subscribers, an additional fee may apply for full text articles.)



[View journal abstract](#)



[View full article](#)

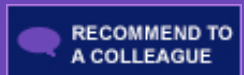
Although early evidence has supported the efficacy of reducing immunosuppression as a therapeutic strategy for transplant-associated skin cancer, clinical thresholds for and risks associated with such reduction have not been well defined. The current study surveyed experienced transplant physicians regarding the appropriate thresholds for consideration in the reduction of immunosuppression, and the risks for rejection and allograft compromise associated with various levels of reduction. A total of 52 transplant physicians reviewed 13 hypothetical patient scenarios with graduated morbidity and mortality risk, and provided their opinions on the degree of immunosuppression reduction necessary and the risks associated with various levels of reduction.

General agreement was reported among renal, liver, and cardiac transplant physicians with respect to the level of immunosuppression reduction warranted by various degrees of skin cancer. As morbidity and mortality from skin cancer rose, the physicians surveyed were more likely to accept the risk to allograft function associated with more aggressive reduction of immunosuppression.

All of the respondents considered reduction of immunosuppression a reasonable adjuvant therapeutic strategy in transplant patients confronted with severe or life-threatening skin cancer. Moreover, assuming that maintenance immunosuppression was already at a level characterized by allograft stability without excess adverse effects, physicians responded unanimously that patients without any skin cancer or precancer did not require immunosuppression reduction. In addition, transplant physicians appeared comfortable with increasing levels of immunosuppression reduction when managing patients with increasing numbers of skin cancer and an increased risk for mortality. Finally, in patients with a high tumor burden or with a high risk for metastatic disease, transplant physicians seemed willing to consider substantial reduction of immunosuppression despite real potential risks to allograft function. The results of this survey may help physicians conceptualize the issues surrounding reduction of immunosuppression but should not be interpreted as direct advice for patient management.

New evidence from Matin and coworkers on melanoma outcomes among organ transplant recipients has provided insight into a small subset of patients in whom alteration of immunosuppression was performed. Information on immunosuppression treatment at the time of melanoma diagnosis was available in 79 of 85 patients (92.9%) in the authors' cohort. Overall, immunosuppression was altered in 34 of 79 renal transplant recipients (43%). As with many prior reports, the nature of the alteration varied considerably between treatment centers. In all cases in which dates were provided (n=29), immunosuppression was altered within the first year following melanoma diagnosis. No significant differences in mortality were observed between the group in whom immunosuppression had been altered compared with the group in whom immunosuppression had not been altered (deaths in 3 of 34 patients [8%] vs 8 of 45 patients [17.8%], respectively; P value from Fisher's exact test, 0.335).<sup>1</sup>

These data, taken together with those from prior reports, highlight the limitation of studies on skin cancer, particularly melanoma, among organ transplant recipients. The most notable limitation is the small number of cases to allow meaningful statistical analysis and



comparisons. Alteration of immunosuppression following a melanoma diagnosis is highly variable, both between treatment centers and even within centers of care. These alterations include reduction or withdrawal of immunosuppression and the switch to mTOR inhibitors. Clearly, the required analysis after separation of these alterations into like groups would lead to even smaller cohorts, thus rendering valid statistical comparisons impossible. Although this evidence may be criticized as being indirect and incomplete, the fact remains that clinical decisions regarding reduction of immunosuppression are being made daily, regardless of the quality of the existing evidence.

1. Matin RN, Mesher D, Proby CM, et al; Skin Care in Organ Transplant Patients, Europe (SCOPE) group. [Melanoma in organ transplant recipients: clinicopathological features and outcome in 100 cases](#). *Am J Transplant*. 2008;8(9):1891-1900..

## ACTIVATION OF mTOR IN PATIENTS WITH MALIGNANT MELANOMA

Karbowiczek M, Spittle CS, Morrison T, Wu H, Henske EP. **mTOR is activated in the majority of malignant melanomas**. *J Invest Dermatol*. 2008;128(4):980-987.

(For non-journal subscribers, an additional fee may apply for full text articles.)



[View journal abstract](#)



[View full article](#)

The objective of this study was to determine whether activation of the kinase/mTOR is associated with human melanoma. To determine whether malignant melanomas exhibit activation of mTOR signaling in vivo, phospho-ribosomal protein S6 immunostaining was performed on tissue microarrays containing a total of 107 melanomas and 67 benign nevi. The phosphorylation of ribosomal protein S6 is widely used as an indicator of mTOR activity in human tumor specimens.

In this study, the authors also investigated whether inappropriate activation of the mTOR pathway is present in melanoma-derived cell lines. Six melanoma cell lines were tested, including a mouse-derived cell line that was used as a control. The authors then attempted to determine whether inappropriate activation of mTOR promotes the growth of melanoma-derived cell lines by testing the effect of mTOR inhibition on proliferation in 3 cell lines with previously identified melanoma-associated mutations. Lastly, since mTOR is directly activated by the small guanosine triphosphatase Ras homolog enriched in the brain (Rheb) in a farnesylation-dependent manner, the study used the farnesyl transferase inhibitor FTI-277 to try to inhibit the proliferation of melanoma-derived cells and thus investigate the mechanism of mTOR activation.

Immunostaining performed on tissue microarrays revealed moderate or strong hyperphosphorylation of ribosomal protein S6 in 78 of 107 melanomas (73%). In contrast, only 3 of 67 benign nevi (4%) were moderately positive and none were strongly positive. Additionally, 5 of the melanoma-derived cell lines showed only a minor increase in phospho-S6 after serum stimulation, suggesting dysregulation of the mTOR pathway and its activation in melanoma-derived cell lines. Rapamycin, a specific inhibitor of the mTOR complex, blocked the phosphorylation of S6 in all cell lines, indicating that regulation of S6 in these cells is mTOR complex 1-dependent.

This study revealed that rapamycin strongly inhibits the growth of 3 melanoma-derived cell lines. Two B-Raf mutant lines showed a statistically significant difference ( $P < 0.05$  Student's *t*-test) in thymidine incorporation after 24 hours of rapamycin exposure, whereas the N-Ras mutant line achieved significance ( $P < 0.05$  Student's *t*-test) after 48 hours. Furthermore, FTI-277 significantly ( $P < 0.05$  Student's *t*-test) inhibited the growth of 3 of the cell lines at the 3-day time point. The small guanosine triphosphatase Rheb directly activates mTOR, and Rheb is farnesylated. Whether farnesylation of Rheb is required for mTOR activation has not yet been completely elucidated. This study found

 **RECOMMEND TO  
A COLLEAGUE**

 **NEWSLETTER  
ARCHIVE**

that phospho-S6 was inhibited by FTI-277 in only 1 cell line, suggesting that the effects of the FTI on melanoma cell growth are primarily independent of Rheb farnesylation.

Novel therapeutic strategies are urgently needed for patients with advanced melanoma. Identification of molecular pathways involved in the pathogenesis and progression of melanoma are a key step toward facilitating directed therapeutic options. Data from this study indicate that mTOR activation is very strongly associated with malignant vs benign melanocytic lesions. These data support the fact that mTOR activation occurs during the pathogenesis of the majority of melanomas. According to Karbowniczek and associates, hyperphosphorylation of ribosomal protein S6 is more strongly associated with malignant vs benign melanocytic lesions than any other single marker. The authors of this study hypothesize that activation of Rheb and mTOR is a common mechanism through which mutations and/or constitutive activation of upstream genes and proteins contributes to melanoma progression.

In conclusion, the results of this study show that activation of mTOR is strongly associated with malignant melanocytic lesions in vivo, that the majority of melanoma-derived cell lines display inappropriate mTOR activation in serum-deprivation conditions, and that inhibition of mTOR blocks the proliferation of melanoma-derived cell lines. Taken together, these data implicate activation of mTOR in the pathogenesis of melanoma, suggesting that Rheb and mTOR may be targets for melanoma therapy. Given the fact that mTOR inhibitors also have immunosuppressive properties and are used in antirejection treatment regimens among solid organ transplant recipients, mTOR may prove to be a dual-action agent for solid organ transplant patients who develop melanoma.

© 2009 JHUSOM, IJHN and *eMedicalDermatology Review*

Created by [DKBmed](#).

## COMPLETE THE POST-TEST

### Step 1.

Click on the appropriate link below. This will take you to the post-test.

### Step 2.

If you have participated in a Johns Hopkins on-line course, login. Otherwise, please register.

### Step 3.

Complete the post-test and course evaluation.

### Step 4.

Print out your certificate.

PHYSICIAN  
POST-TEST

NURSE  
POST-TEST