Chemoprevention and Treatment of Experimental Cowden’s Disease by mTOR Inhibition with Rapamycin

Cristiane H. Squarize, Rogerio M. Castilho, and J. Silvio Gutkind

Oral and Pharyngeal Cancer Branch, National Institute of Dental and Craniofacial Research, NIH, Bethesda, Maryland

Abstract

Cowden’s disease is an autosomal dominant disorder characterized by the development of multiple mucocutaneous lesions and benign tumors, and enhanced cancer predisposition. Most Cowden’s disease patients harbor inactivating mutations in the PTEN tumor suppressor gene which encodes a lipid phosphatase, PTEN, which restrains the phosphatidylinositol 3-kinase–Akt signaling pathway. We observed that the epithelial-specific deletion of Pten in mice causes multiple hyperproliferative and tumor lesions that strikingly resemble Cowden’s disease. This animal model system provided an opportunity to explore novel therapeutic approaches in Cowden’s disease. Indeed, we show here that rapamycin administration, which inhibits a key downstream target of Akt, mammalian target of rapamycin (mTOR), promotes the rapid regression of advanced mucocutaneous lesions. Furthermore, when administered before disease manifestation, rapamycin can halt the development of Cowden’s disease–like lesions, thereby prolonging animal survival. These findings suggest that mTOR inhibition with rapamycin may represent a suitable therapeutic option for the chemoprevention and treatment of Cowden disease patients and other tumor syndromes that involve defective PTEN function. [Cancer Res 2008;68(17):7066–72]

Introduction

Cowden’s disease is an autosomal dominant disorder characterized by the development of multiple mucocutaneous lesions and benign tumors, and by the predisposition to a variety of malignancies, particularly breast and thyroid cancers (1–4). The Cowden’s disease gene locus has been mapped to the chromosome 10q22-23 in which the PTEN gene is located (5–8). PTEN encodes a lipid phosphatase, PTEN, which is a negative regulator of the phosphatidylinositol 3-kinase (PI3K) pathway by converting phosphatidylinositol 3,4,5-triphosphate (PIP3) into phosphatidylinositol 4,5-bisphosphate (PIP2). (9–11). Underscoring the importance of PTEN as a tumor suppressor gene, germline mutations of PTEN have been linked to several autosomal dominant hamartoma syndromes including Cowden’s disease (OMIM:608430), Bannayan-Riley-Ruvalcaba syndrome (OMIM:153480), and Lhermitte-Duclos syndrome (OMIM:158350), which are all characterized by the presence of benign tumors, known as hamartomas, in multiple organs and an increased susceptibility to developing a variety of malignancies (reviewed in ref. 12)

In the case of Cowden’s disease, PTEN germline mutations are found in 80% of the patients, either in the PTEN coding sequence, in the PTEN promoter, or in its 5’ and 3’ untranslated region resulting in inhibition of translation or a catalytically inactive, immature, or unstable PTEN protein, which may undergo rapid degradation (10, 12). Pten heterozygosity and tissue-specific deletion in mice leads to hyperplastic and dysplastic changes in the prostate, colon, and skin, and to spontaneous tumor development, supporting the notion that PTEN plays a causal role in hamartoma syndromes (13–19). Cells exhibiting decreased PTEN activity are not able to restrain the growth promoting properties of PI3K and its lipid product, PIP3 (10, 11, 20). One of the best studied downstream targets of PI3K is the serine-threonine kinase Akt, which, upon activation by PIP3, promotes cell proliferation and survival by phosphorylating multiple protein targets, thereby controlling cell growth, protein translation, cell metabolism, and program cell death (21, 22).

As Cowden’s disease is characterized by the high incidence epithelial derived tumors, we selectively inactivated a floxed Pten allele in mice by the expression of Cre recombinase under the control of the keratin 14 (K14) promoter, which is expressed in hair follicles, glandular ducts, epidermis, and other epithelial cells (23, 24). Although mice developed normally, and newborn mice did not exhibit any obvious phenotype, Pten deletion in epithelial cells led to the development of multiple dermal lesions and breast and thyroid tumors as age progressed, strikingly resembling Cowden’s disease. This animal model provided an opportunity to explore the efficacy of interfering with the PI3K/Akt pathway as a therapeutic approach in this hamartoma syndrome. Indeed, we show here that the pharmacologic inhibition of one particular downstream target of Akt, mammalian target of rapamycin (mTOR), by the prolonged treatment with rapamycin promoted the rapid regression of advanced Cowden’s disease–like lesions. Furthermore, we found that by initiating the chronic administration of rapamycin before the appearance of disease manifestation in mice, in which Pten has been conditionally deleted, was sufficient to prevent the development of Cowden’s disease–like lesions, thereby prolonging remarkably animal survival. Thus, these findings suggest that the blockade of mTOR with rapamycin and its analogues may represent a suitable therapeutic option for the chemoprevention and treatment of Cowden disease’s patients.

Materials and Methods

Experimental mice. All animal studies were carried out according to NIH approved protocols, in compliance with the Guide for the Care and Use of Laboratory Animals. PtenF/F mice (The Jackson Laboratory; ref. 25) were crossed with K14Cre mice (24) to generate K14Cre PtenF/+ heterozygous mice, which were further crossed with PtenF/F mice to generate K14Cre PtenF/F (homozygous), K14Cre PtenF/+ PtenF/F, and PtenF/F mice, all in the
same litter. The mice had free access to water and pellet stock diet, with the addition of high-fat supplement, when needed. Genotyping was performed on tail biopsies using a PCR assay with primers P1 (5′ actcaaggcagggatgagc 3′) and P2 (5′ cacggataagtctgagctctgc 3′) for Pten<sup>flaloxx</sup>, and primers P3 (5′ cacggataagtctgagctctgc 3′) and P4 (5′ cacggataagtctgagctctgc 3′) for K14-Cre.

**Rapamycin administration.** Rapamycin (LC Laboratories) was reconstituted in absolute ethanol at 10 mg mL<sup>-1</sup> and stored at −20°C. Rapamycin was diluted in 5.2% Tween 80 (Sigma) and 5.2% polyethylene-glycol (PEG-400; Hampton Research; ref. 26), and injected i.p., 1 mg/kg every other day.

**Culture of primary keratinocytes and Western blotting.** Murine keratinocytes were isolated as described (23), grown in KRB-2 medium (Cambrex). After lyses, protein concentrations were determined and 30 g of proteins were separated on 10% SDS-PAGE, transferred to nitrocellulose membranes, blocked with 5% milk protein, and incubated with primary antibodies Akt, phospho-specific Akt (pAkt<sub>Ser473</sub> and pAkt<sub>Thr308</sub>), and S6 (pS6; Cell Signaling Technology), PTEN (Cascade Bioscience), and tubulin (Santa Cruz Biotechnology), as previously described (27). Western blot signals were quantitated by using the NIH Image J software.

**Histology and immunohistochemistry of tissue sections.** H&E staining was performed on formalin-fixed and paraffin-embedded 4-μm serial sections according to standard procedures. Immunohistochemistry was performed on these paraffin-embedded and frozen tissue sections using antibodies pAkt<sub>Ser473</sub>, pAkt<sub>Thr308</sub>, pS6 (Cell Signaling Technology), and proliferating cell nuclear antigen (PCNA; Zymed Laboratories) as described previously (26, 28). Quantitative analysis of the staining intensity was performed by using the NIH Image J software. Procedure periodic acid-Schiff (PAS) staining (Sigma-Aldrich) was performed as described by the manufacturer.

**Statistical analysis.** Comparison of the Kaplan-Meier survival analysis was performed with the logrank test. Statistical analysis of the staining for PCNA, pAkt<sub>Ser473</sub>, pAkt<sub>Thr308</sub>, pS6, and the body weight was performed by ANOVA One-way, followed by the Bonferroni’s multiple comparison tests using GraphPad Prism 4.03 (GraphPad Software).

**Results**

**Excision of Pten recapitulates features of Cowden’s disease.** We generated epithelial-specific Pten conditional knockout mice by crossing mice harboring a floxed Pten allele containing two loxP sites (Pten<sup>F<sub>loxP</sub>F<sub>loxP</sub></sup>) with mice expressing the Cre recombinase under the control of the K14 promoter (K14-Cre). K14-Cre Pten<sup>F<sub>loxP</sub>F<sub>loxP</sub></sup> heterozygous mice were backcrossed with Pten<sup>F<sub>loxP</sub>F<sub>loxP</sub></sup> mice, and littermates that inherited some but not all of the above alleles served as controls. K14-Cre Pten<sup>F<sub>loxP</sub>F<sub>loxP</sub></sup> mice were undistinguishable from the littermates at birth. However, at ages 6 days, the skin was wrinkled and flaky when compared with heterozygous K14Cre Pten<sup>F<sub>loxP</sub>F<sub>loxP</sub></sup> and control mice, and by ages 11 days, the hair shafts had a disheveled appearance (data not shown). The animals progressively developed multiple hyperproliferative lesions, ranging from mucocutaneous lesions (95%; 41 of 44 mice) to tumor formation (Fig. 1A, middle). Histologically, most facial and periauricular areas displayed verrucous and hyperkeratotic lesions also seen in the punctuate palmoplantar keratosis of the paws (Supplementary Fig. S1A; paw).

**Deletion of Pten compromises animal survival.** Initially, the offspring from mating K14Cre Pten<sup>F<sub>loxP</sub>F<sub>loxP</sub></sup> mice with Pten<sup>F<sub>loxP</sub>F<sub>loxP</sub></sup> mice followed the expected Mendelian distribution (Supplementary Fig. S2A). Although rapid death was initially observed in K14Cre

![Figure 1.](https://example.com/figure1.png)
Table 1. Manifestations of Cowden’s syndrome

<table>
<thead>
<tr>
<th>Pathognomonic criteria</th>
<th>Human</th>
<th>Animal model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muco-cutaneous lesions</td>
<td>90–100%</td>
<td>95% (41/44)</td>
</tr>
<tr>
<td>Facial papillomatous lesions</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Trichilemmomas</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acral keratoses</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(ears, limbs, and fingers)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmo-plantar keratoses</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Oral mucosa papillomatosis</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Major criteria**

- **Breast cancer** 30–76% 36% (8/22)
- **Thyroid cancer** 3–10% 2% (2/16)
- **Other lesions and symptoms**
  - Intestinal polyps 44% —
  - Genitourinary lesions 5–44% 4.5% (2/16)
  - Thyroid Abnormalities 50–67% 56% (9/16)

Pten<sup>F/F</sup> mice in the first few days of life (Fig. 1B; Supplementary Fig. S2A), their survival was much greater than observed when using Cre driven by the K5 promoter (14). Although K14- and K5-driven gene expression are expected to have somehow overlapping tissue specificity (29), K14Cre Pten<sup>F/F</sup> mice did not develop esophageal hyperplasia, which could compromise the survival of K5Cre mice. In addition, we were able to achieve an increase in animal survival of K14Cre Pten<sup>F/F</sup> mice by removing littermate competition and extending the weaning period (Supplementary Fig. S2A). Under these optimized breeding conditions, most animals survived until weaning, and 40% of the mice survived beyond ages 3 months, although the life span of K14Cre Pten<sup>F/F</sup> mice did not exceed 250 days (Fig. 1B; Supplementary Fig. S2A). Decreased survival was also present in heterozygous K14Cre Pten<sup>F/+</sup> mice, which died or had to be sacrificed because of morbidity (Fig. 1B). Nonetheless, the ability to extend the survival of K14Cre Pten<sup>F/F</sup> mice for up to ages 9 months enabled us to explore in detail the nature of the pathologic conditions caused by Pten deletion in the epithelial compartment of mice.

Hyperproliferative and tumoral lesions in K14Cre Pten<sup>F/F</sup> mice. As described above, several cutaneous lesions could be readily observed during examination of K14Cre Pten<sup>F/F</sup> mice. They include the unique presence of trichilemmomas, a pathognomonic sign of Cowden’s Disease (2) that resembles blown-up hair follicles, which often exhibit cylindrical or lobular proliferation and PAS-positive proliferating glycerogen-rich clear cells (Fig. 2A, top). Besides numerous skin alterations, Cowden’s disease is characterized by thyroid multinodular goiter, adenomas, and increased risk for thyroid cancer (4, 8). Indeed, homozygous deletion of Pten resulted in alterations in the thyroid gland of K14Cre Pten<sup>F/F</sup> mice (n = 16), including multinodular goiters (56%; 9 of 16 mice analyzed) and thyroid tumors (12%; 2 of 16 mice analyzed) with a follicular aspect (Fig. 2A, bottom; Table 1). Patients harboring PTEN deletions and mutations also often develop fibroepithelial, fibrocystic disease, virginal hypertrophy of the breast, and malformations of nipples and areolae (3, 4, 30). This was reflected in K14Cre Pten<sup>F/F</sup> mice, 80% (29 of 36 mice analyzed) of which displayed morphologic alterations in the nipples. Multiple mammary gland tumors were also observed in the thoracic and abdominal/inguinal mammary glands of K14Cre Pten<sup>F/F</sup> mice (11% 4 of 36 mice analyzed; Fig. 2B; Table 1). This was even more remarkable in K14Cre Pten<sup>F/+</sup> mice (36%; 8 of 22 mice analyzed), as their extended survival enabled the development of larger tumor masses. In both cases, lesions were characterized by the presence of prominent intraluminal and ductal proliferation (Fig. 2B, b). Histologic features of breast tumors ranged from fibroadenomas (Fig. 2B, c) to adenocarcinomas and ductal carcinomas with dense hyaline collagen or dense fibrosis replacing the intralobular stroma (Fig. 2B, e and f).

Reversion of Cowden’s disease-like lesions by mTOR inhibition. Activation of Akt involves its recruitment to the membrane by binding PIP<sub>3</sub> and the initial phosphorylation of threonine 308 (Thr308) in its activation loop by PDK1 (22, 31). Subsequently, Akt is phosphorylated in serine 473 (Ser473) by one of its downstream targets, the atypical kinase mTOR, thereby increasing its activity (31). mTOR in turn regulates protein

![Figure 2. Epithelial excision of Pten leads to tumor formation. Examples of H&E histologic sections from control and conditional epithelial Pten deletion as indicated. A, typical hair follicle (a) and hair follicle tumor formation displaying trichilemmomas of cylindrical type (b and c, black arrow) resembling typical blown-up hair and exhibiting the presence of glycerogen-rich clear cells positive for PAS (c, white arrow). Normal thyroid (d) and goiter displaying widespread follicular enlargement homogeneously filled with colloid (e) and tumor formation with focal hyperplasia, hypercellularity with solid or microfollicular pattern, and little or no colloid among follicles (f). B, normal breast tissue from adult mice showing dispersed mammary ducts among adipose tissue (a, d). Note the intraluminal proliferation in the mammary duct of K14Cre Pten<sup>F/F</sup> mice (b) and the proliferation of epithelial cells forming cystic dilated duct-like spaces surrounded by a well-demarcated capsule (c). Mammary tumors in Pten-deleted mice also displayed a thickened basal lamina surrounding the compressed and distorted ducts among the densely hyaline collagen (e). In other cases, dense fibrosis diffusely replaces the interlobular stroma (f).](Image)
which was quite elevated in Pten-deficient mice when compared with littermate controls. In K14Cre Pten F/F mice, when compared with vehicle or rapamycin. Note the elevated phosphorylation of pS6 and Akt in Ser473, and PCNA in K14Cre Pten F/F mice. Upon treatment, pS6, pAkt Ser473 levels, and PCNA nuclear staining were notably reduced. pAkt Thr308, which is present in the nucleus of epithelial cells in K14Cre Pten F/F mice, shifted to the membrane in rapamycin-treated mice. C. Representative Western blot analysis of primary culture from mice for molecules whose activity is regulated by PTEN and tubulin, as a loading control, in lysates from primary cultures of keratinocytes isolated from control (c), K14Cre Pten F/F (f/+), and K14Cre Pten F/F (f/f) mice (n = 3 independent experiments per genotype). Cells were treated with vehicle or rapamycin, as indicated. PTEN levels were reduced in K14Cre Pten F/F and almost absent in K14Cre Pten F/F, which presents increased levels of both pAkt Thr308 and pAkt Ser473. Rapamycin effectively ablates S6 phosphorylation, normalizes pAkt Ser473, and increases pAkt Thr308 in homozygous K14Cre Pten F/F mice when compared with heterozygous and control mice. C, quantitative analysis of pAkt Ser473, pAkt Thr308, and pS6, as fold increase of the control mice (n = 3) normalized by the total amount of protein and displayed as fold increase of the control mice (C, bottom, white bar).

Figure 3. Rapamycin treatment reverses Cowden’s disease–like lesions and modulates mTOR pathway in K14Cre Pten F/F–derived tumors. A, representative examples of rapamycin-treated mice (n = 4) within 9 d of treatment. Rapamycin profoundly decreases well-established mucocutaneous lesions in the face (top) and paws (bottom) of the same K14Cre Pten F/F mouse. B, representative example of immunohistochemical staining for pAkt Thr308, pAkt Ser473, pS6, and PCNA in the epithelium from control and K14Cre Pten F/F mice treated with vehicle or rapamycin. Note the elevated phosphorylation of pS6 and Akt in Ser473, and PCNA in K14Cre Pten F/F mice. Upon treatment, pS6, pAkt Ser473 levels, and PCNA nuclear staining were notably reduced. pAkt Thr308, which is present in the nucleus of epithelial cells in K14Cre Pten F/F mice, shifted to the membrane in rapamycin-treated mice. C, representative Western blot analysis of primary culture from mice for molecules whose activity is regulated by PTEN and tubulin, as a loading control, in lysates from primary cultures of keratinocytes isolated from control (c), K14Cre Pten F/F (f/+), and K14Cre Pten F/F (f/f) mice (n = 3 independent experiments per genotype). Cells were treated with vehicle or rapamycin, as indicated. PTEN levels were reduced in K14Cre Pten F/F and almost absent in K14Cre Pten F/F, which presents increased levels of both pAkt Thr308 and pAkt Ser473. Rapamycin effectively ablates S6 phosphorylation, normalizes pAkt Ser473, and increases pAkt Thr308 in homozygous K14Cre Pten F/F mice when compared with heterozygous and control mice. C, quantitative analysis of pAkt Ser473, pAkt Thr308, and pS6, as fold increase of the control mice (C, bottom, white bar).

translation by phosphorylating 4EBP, an inhibitory factor activation of Akt (38), similar to that reported during recent clinical trials with rapamycin in PTEN-deficient glioblastoma patients (41). Of interest, however, this active Akt may not be able to be released from the membrane in cells that accumulate PI(3)P due to the absence of Pten phosphatase activity, as judged by its membrane accumulation (Fig. 3B, middle).

Elevated levels of pS6 and the effect of rapamycin on pAkt Thr308 were also observed in primary cultures of keratinocytes isolated from K14Cre Pten F/F mice. As expected, Pten levels were reduced in cells isolated from heterozygous K14Cre Pten F/F mice, and almost absent in keratinocytes from K14Cre Pten F/F homozygous mice.
We observed increased levels of both pAktSer473 and pS6 in K14Cre PtenF/F homozygous mice. Rapamycin treatment lead to a complete ablation of S6 phosphorylation, although it had only a limited effect on pAktSer473 levels, aligned again with the direct effect of rapamycin on the mTORC1 complex after short time treatment. However, rapamycin provoked an increase in pAktThr308 in primary cultures from Pten-deficient mice when compared with those derived from heterozygous and control mice (Fig. 3C). Thus, the effects of rapamycin on signaling events in the epithelial compartment of the skin of K14Cre PtenF/F mice likely represent a primary effect on the targeted cells, rather than resulting from alterations caused by mTOR inhibition in the stroma.

**Rapamycin as a chemoprevention agent for experimental Cowden’s disease.** Over 90% of individuals affected with Cowden’s disease are believed to manifest clinical signs of the disease by the ages 20 years; 99% of the affected individuals develop mucocutaneous lesions by the end of the third decade, although other clinical manifestations may be present; and tumor formation is usually detected at the beginning of the fourth decade (Fig. 4; refs. 1–4). Of interest, as mice age, K14Cre PtenF/F animals acquired a phenotype that closely resembles the progression of Cowden’s disease (Fig. 4; Table 1). Thus, we asked whether rapamycin administration before the appearance of disease manifestation could prevent the development of Cowden’s disease–like lesions in mice already harboring Pten deletions. For these experiments, we administered a clinically relevant low dose of rapamycin (37) starting at ages 5 days, and compared disease progression in the treated animals to their littermate controls (n = 13 per group). There were no statistically significant differences in the body weight when comparing control mice treated with the rapamycin inhibitor and vehicle (Fig. 4C). The K14Cre PtenF/F mice treated with vehicle (20.9 ± 2.8 g) were slightly smaller then their control littermates (28.1 ± 2.9 g) but gained weight similar to control mice upon rapamycin treatment (24.1 ± 2.5 g; Fig. 4C). Furthermore, rapamycin treatment prevented the development of dermatologic lesions, including facial papules, oral papules, acral, and palmo-plantar keratoses, and increased the life span of K14Cre PtenF/F mice (Fig. 4A and B). This reduction in the mortality of K14Cre PtenF/F mice was quite remarkable (vehicle control; median survival, 94 days; rapamycin: median survival, >320 days; P < 0.0001; Fig. 4B), suggesting that mTOR inhibition may represent a suitable chemopreventive strategy to halt Cowden’s disease progression (Fig. 4D).

**Discussion**

Cowden’s disease was named after the first described patient, Rachael Cowden, in 1963 (1). The discovery of PTEN germline...
somatic mutations in the majority of Cowden's disease patients have provided an opportunity for the early diagnosis to individuals that are susceptible to the development of this debilitating and cancer-prone syndrome (5–8). Aligned with the key role of PTEN in Cowden's disease syndrome, we were able to recapitulate most of the pathognomonic lesions characterizing Cowden's disease, including trichilemmoma, acral keratoses, papillomatous, and mucosal lesions, and even breast and thyroid alterations and tumors by deleting Pten in stratified and ductal epithelial cells using K14Cre mice, which was combined with the optimization of the housing conditions to extend the life span of the affected mice. The availability of this animal model provided a unique opportunity to explore the ability to interfere with PTEN downstream molecules as potential targets for therapeutic intervention in Cowden's disease.

Reduced PTEN function, and thus elevated PIP₃ accumulation, can result in altered activity of a PI3K-dependent signaling network, which ultimately promotes disease progression (21, 22). Although inhibiting PI3K activity would be a good candidate to limit PIP₃, and as a result compensate for PTEN reduced activity, currently, PI3K inhibitors may have undesirable side effects that limit their clinical use (42). Among the many biochemical routes regulated by PI3K, the Akt-mTOR pathway has recently emerged as a key component of proliferative pathways activated downstream from PI3K and PTEN (34, 35, 43). In this regard, loss of mTOR is epistatic to Pten loss in drosophila megalogaster (44, 45). Furthermore, the oncogenic activity of Akt seems to depend on mTOR, and many sporadic tumors involving PTEN deletions and inactivating mutations are highly sensitive to rapamycin treatment that blocks mTOR (43, 46, 47). Indeed, we observed elevated activity of Akt and mTOR in hyperproliferative lesions resulting from Pten deletion. Thus, considering that propylthiouracil is often recommended (48) and there is no approved therapy available for Cowden's disease, we explored the consequences of mTOR inhibition with rapamycin in this genetically defined animal model. We observed that rapamycin treatment can rapidly revert the mucocutaneous papillomatous lesions in the face and limbs, acral keratosis, and deformities of nipples, among others, concomitant with a marked decreased of the elevated levels of pS6, which served as a suitable biomarker of drug efficacy in the target tissues. Furthermore, the early treatment with rapamycin prevented the development of Cowden's disease–like lesion in mice in which Pten was excised, thus dramatically increasing their life expectancy.

The use of rapamycin has been approved by the Food and Drug Administration (FDA) in 1999 to prevent renal transplantation rejection (49). Since then, many analogues of rapamycin have been developed, some of which have increased bioavailability and are well-tolerated with reduced side effects, including lack of immunesuppressive activity at doses that are effective in blocking mTOR (35, 49). Rapamycin (41) and many of its analogues (rapalogs), includingCCI-779 (temsirolimus), RAD001 (everolimus), and AP23573, are in clinical trials for a variety of tumor types, and CCI-779 has been recently approved by FDA for the treatment of renal carcinoma patients (50). Collectively, the extensive experience with the use of rapalogs in the clinic and the key role of mTOR in Cowden's disease progression may provide the rationale for the early clinical evaluation of rapamycin and its analogues as a molecular-targeted chemopreventive strategy for Cowden's disease and others tumor syndromes that involve defective PTEN function.

Disclosure of Potential Conflicts of Interest

The authors declare that they have no competing financial interests.

Acknowledgments

Received 3/13/2008; revised 5/28/2008; accepted 7/1/2008.

Grant support: Intramural Research Program of NIH, National Institute of Dental, and Craniofacial Research.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

We thank Alfred Molinolo and Thomas Bugge for their critical comments.

References


www.aacrjournals.org
7071

Published OnlineFirst July 1, 2008

Cowden's Disease Chemoprevention by Targeting mTOR

Downloaded from cancerres.aacrjournals.org on June 9, 2017. © 2008 American Association for Cancer Research.


Chemoprevention and Treatment of Experimental Cowden's Disease by mTOR Inhibition with Rapamycin

Cristiane H. Squarize, Rogerio M. Castilho and J. Silvio Gutkind


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/68/17/7066

Supplementary Material
Access the most recent supplemental material at:
http://cancerres.aacrjournals.org/content/suppl/2008/08/21/68.17.7066.DC1

Cited articles
This article cites 50 articles, 16 of which you can access for free at:
http://cancerres.aacrjournals.org/content/68/17/7066.full#ref-list-1

Citing articles
This article has been cited by 15 HighWire-hosted articles. Access the articles at:
http://cancerres.aacrjournals.org/content/68/17/7066.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.