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Hormone Therapy for the Treatment of Patients with Malignant Salivary Gland Tumor (MSGT)

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1. Introduction

Malignant salivary gland tumors (MSGTs) account for 2-6% of all head and neck cancers (Glisson et al., 2004; Milano et al., 2007). Despite their rarity, MSGTs have been of great interest because of their wide variety of pathological features and high rates of metastasis, which result in poor prognoses. Surgical resection followed by radiation therapy is the primary therapy for this malignancy. Adjuvant therapy is reserved for the management of local recurrence no longer amenable to additional local therapy and for metastasis. Based on studies of other types of tumors, particularly breast cancer, the expression and function of sex steroid hormone receptors in cancer have been extensively studied and the findings applied to diagnosis and treatment (Clarke & Sutherland, 1990; Kester et al., 1997). Although a number of studies have been published, the rationale for hormone therapy of MSGTs remains controversial because of disparate results and an insufficient number of cases. However, some recent studies have shown that certain salivary gland neoplasms are similar to breast cancer, not only in terms of their pathological features, but also at the molecular level (Pia-Foschini, 2003; Wick et al., 1998; Yoshimura et al., 2007). Here, we shed light on the biological similarity between MSGTs and certain types of breast cancer, and describe the potential use of hormone and additional therapies for MSGTs.

2. The role of sex steroid hormone receptors in cancer therapy

The function of sex steroid hormone receptors in breast cancer has been extensively studied and the findings applied to diagnosis and treatment (Clarke & Sutherland, 1990; Kester et al., 1997) Estrogen stimulates cell proliferation of breast epithelial cells, and the close relationship between the expression of estrogen receptor (ER) and the prognosis of breast cancer has been well characterized (Ma et al., 2009). Progesterone levels fluctuate during the menstrual cycle and regulate cell proliferation and differentiation; however, less is known regarding its role in breast cancer (Jeng et al., 1992; Sutherland et al., 1988; van der Burg et al., 1992) We have previously reported that introducing progesterone receptor (PR) into hormone-independent breast cancer cells significantly suppresses their proliferative and invasive activities upon progesterone treatment (Sumida et al., 2004). Several drugs, such as

Tamoxifen, an estrogen receptor antagonist, and a synthetic progestin similar to progesterone, are considered to be effective at inhibiting tumor cell proliferation. These drugs are given as adjuvant therapies to breast cancer patients when immunohistochemical staining of their tumor tissue indicates that >10% of the breast cancer cells express ER or PR (Horwitz, 1993; Williams et al., 2007). Molecular-targeted drug therapy is generally less toxic than traditional chemotherapy; however, some studies have reported severe side effects, and carefully designed and regulated clinical trials are necessary to confirm their safety. Moreover, these types of therapies are not viable when a tumor expresses a low level of a molecular target such as a receptor (Ismail-Khanet al., 2010). This problem is exemplified by breast cancers that do not express ER, PR, or HER2 receptors, that is, in triple negative cases. It is a challenge for clinicians to provide efficacious treatments for this patient population.

Sex steroid hormone therapy in prostate cancers is based on their high sensitivity to androgen inhibition. The most common hormone therapy is initiated by reducing the concentration of circulating androgens through surgical or medical castration and/or by administering anti-androgens such as flutamide or bicalutamide (Klotz et al., 2005; Miyake et al., 2005). However, in almost all patients, the efficacy of the treatment decreases over time as the tumor becomes "androgen-refractory" (Yuan et al., 2009). As a result, these patients develop distant metastases, such as in the bone, which eventually proves fatal to the patient. Therefore, the molecular events that control the transition from androgen-sensitive prostate cancer to androgen-refractory prostate cancer need to be elucidated.

Accumulating evidence suggests that the androgen receptor (AR) plays a critical role in regulating the growth of both androgen-sensitive and androgen-refractory prostate cancer (Chen et al., 2004; Debes et al., 2004; Grossmann et al., 2001; Hara et al., 2003; Scher et al., 2005; Taplin et al., 2004). In addition, recent studies have shown that the AR can regulate invasion and metastasis (Hara et al., 2008). In AR-negative cell lines such as PC3 and DU145, it has been shown that forced AR expression decreases their invasive properties and treatment with androgen further reduces invasion by these cells (Bonaccorsi et al., 2000; Cinar et al., 2001). Moreover, it has been reported that hormone-refractory prostate cancers have a variety of AR alterations that are either not found in hormone-naive tumors or are found at a lower frequency (Taplin et al., 2004). A more recent investigation demonstrated that forced expression of AR in a subline of a metastatic androgen-dependent prostate cancer cell line led to increased invasion (Hara et al., 2008). It is clear that a more detailed understanding of the AR alterations in the evolution of androgen-refractory prostate cancer is needed to help drive the development of potential new therapies.

Few studies of ovarian and colon cancer have addressed the potential application of hormone therapies (Burkman, 2002). In ovarian cancer, the use of estrogen as a menopausal therapy has frequently been associated with an increased risk of ovarian cancer, and there is still conflicting evidence regarding the impact of hormone therapy in terms of decreasing the risk of cancer (Greiser et al., 2010). A recent study, however, suggested that this problem can be circumvented by co-administering progestin and estrogen (Pearce et al., 2009). Further, experiments in culture showed that progesterone reduced the proliferation of both benign and malignant ovarian tumor cells (Zhou et al., 2002). Therefore, progestin might be a key factor for preventing and suppressing ovarian cancer cell growth. In contrast to ovarian cancer, estrogen appears to have protective effects against colon cancer (Kennelly et al., 2008). However, the role of hormone replacement therapy with estrogen for the treatment of colon cancer is poorly understood, and further analyses are needed.

3. Pathological and biological similarities between MSGTs and breast cancer

Mammary and salivary glands are tubulo-acinar exocrine glands that share similar morphological characteristics. Similar histological features are observed when the tumors arising from these 2 sites are compared (Camelo-Piragua et al., 2009; Hellquist et al., 1994; Marchio et al., 2010; Pia-Foschini et al., 2003). Although the cancers differ in terms of their incidence and clinical behavior, certain biological features have been described in both entities and potential common therapeutic approaches have been considered. The WHO classification of MSGTs lists more than 20 different histological subtypes (Laurie et al., 2006; Milano et al., 2007). The majority of these are divided into 2 groups—those of secretory duct origin (including mucoepidermoid carcinoma [MEC] and salivary duct carcinoma [SDC]) and those of intercalated origin (including adenoid cystic carcinoma [ACC]) (Batsakis et al., 1989; Dardick et al., 1987). Most of these tumors occur in the parotid gland (70%), and less than 25% are malignant (Glisson et al., 2004). Although the incidence of tumors at other sites such as the submandibular, sublingual, and minor salivary glands is less common, malignancy at these sites is higher, approximating 50% (Glisson et al., 2004). Most aggressive breast cancers are composed of invasive ductal carcinomas, and other histologic features such as MEC and ACC are relatively rare. Below, we briefly describe some of the types of MSGTs that display features (at the morphological and molecular level) that they have in common with breast cancers, and could therefore provide potential common therapeutic strategies.

3.1 Mucoepidermoid carcinoma (MEC)

MEC is the most common salivary gland neoplasm, accounting for 29–34% of all malignancies of the major and minor salivary glands (Milano et al., 2007). These tumors grow slowly and present as painless masses in most cases. They are primarily composed of intermediate, mucous, and epidermoid cells. The cell types are classified histologically as low-, intermediate-, and high-grade; 5-year overall survival (OS) varies from 92% to 100% for low-grade tumors, 62% to 92% for intermediate-grade tumors, and 0% to 43% for high-grade tumors (Pires et al., 2004). High-grade MEC is an aggressive malignancy, characterized by high rates of local recurrence and distant metastasis. On the contrary, low-grade MECs generally do not metastasize. MEC of the breast is a rare entity with an estimated incidence of 0.2% and is composed of a mixture of basaloid, intermediate, epidermoid, and mucinous cells (Camelo-Piragua et al., 2009; Fisher et al., 1983). Since Patchefsky et al. first described breast MEC in 1979, only 28 cases have been reported (Berry et al., 1998; Chang et al., 1998; Di Tommaso et al., 2004; Fisher et al., 1983; Gomez-Aracil et al., 2006; Hanna et al., 1985; Hastrup et al., 1985; Hornychova et al., 2007; Kovi et al., 1981; Leong et al., 1985; Luchtrath et al., 1989; Markopoulos et al., 1998; Patchefsky et al., 1979; Pettinato et al., 1989; Ratanarapee et al., 1983; Tjalma et al., 2002). Because of its rarity, the prognosis remains controversial debatable matter. However, MECs from the breasts and salivary glands have been shown to share similar biological features and morphologies (Camelo-Piragua et al., 2009). Researchers have classified breast MECs into 3 grades by using the same grading system as for salivary gland tumors and have demonstrated that high-grade tumors are associated with high mortality as a result of lymph node and distant metastases. These results suggest that MECs from both mammary and salivary glands have similar morphological features, and thus could have similar treatment strategies. Further, a common cytogenetic alteration of breast and salivary MECs has been reported. A reciprocal

translocation t(11;19)(q21;p13) (MAML2: MECT) was identified in breast MEC; this is the most frequent genetic alteration in the salivary glands (Tonon et al., 2003). The translocation creates a fusion product (MAML2: MECT1) that activates transcription of cAMP/CREB target genes (Tonon et al., 2003; Tonon et al., 2004). Another report noted that patients in whom the protein fusion gene is expressed have a significantly lower risk of death compared to patients without the fusion protein MAML2:MECT1 (Behboudi et al., 2006). It has also been shown that other subtypes of breast cancer are negative for this gene, suggesting that this fusion gene is specific to MEC. This translocation is likely to be a promising marker of MECs from both the mammary and salivary glands (Nordkvist et al., 1994).

3.2 Adenoid cystic carcinoma (ACC)

ACCs account for 22% of MSGTs (Hotte et al., 2005). There are 3 histological subtypes: tubular; cribriform; and solid (Da Silva et al., 2009; Pia-Foschini et al., 2003). In contrast to the squamous cell carcinomas that account for the vast majority of head and neck malignancies, ACC often spreads systemically, especially to the lung and bone, and the metastatic proportion of this type of neoplasm is 24–55% (Dodd et al., 2006). Because of the high metastatic rate, prognosis is poor. The 10-year OS is 39–55% and the 20-year OS is 21–25% (Dodd et al., 2006).

On the other hand, breast ACC is a rare malignancy, accounting for 0.1–1% of all breast cancers (Marchio et al., 2010). In addition, these neoplasms show different clinical behaviors than their salivary gland counterparts. The 10-year OS is >90%, and lymph node and distant metastases are generally rare (Marchio et al., 2010). However, the histological features of breast ACCs are very similar to ACCs originating from the salivary glands (as shown in Fig. 1). Ro et al. applied the same grading system to ACCs from both types of tissues, and both breast and salivary gland tumors are characterized by expression of c-KIT and share a common chromosomal translocation t(6;9) leading to the fusion gene MYB-NFIB (Marchio et al., 2010; Persson et al., 2009; Ro et al., 1987). c-KIT has been shown to be expressed in 80–100% of ACCs of the salivary glands and in almost all ACCs from the breast (Azoulay et al., 2005; Crisi et al., 2005; Edwards et al., 2003; Holst et al., 1999; Jeng et al., 2000; Mastropasqua et al., 2005; Vila et al., 2009; Weigelt et al., 2008). The genetic alteration t(6;9)(q22-23;p23-24) was first identified as a characteristic of salivary gland ACCs (Nordkvist et al., 1994). Since then, the same translocation has been detected in breast tumors (Persson et al., 2009). The fusion gene is highly expressed in proliferating cells and is downregulated as the cells become more differentiated. Therefore, this gene may provide new therapeutic approaches for the management of ACCs.

3.3 Salivary duct carcinoma (SDC)

SDC is a rare and highly aggressive neoplasm with histologic features very similar to that of invasive ductal carcinoma of the breast (IDC) (Barneset al., 1994; Hellquist et al., 1994; Kleinsasser et al., 1968). SDC is generally more aggressive and has lower survival rates than other MSGTs. The epithelium tends to form cribriform, papillary, and solid growth patterns along with duct-like structures (Hellquist et al., 1994). The morphology of SDC is characterized by cuboidal and polygonal cells forming distended ducts and solid nests (often with central necrosis) that are very similar to comedocarcinoma (Hellquist et al., 1994). In addition to the histopathological resemblance, both entities have similar clinical behaviors, that is, they have highly metastatic features leading to a poor prognosis. A wide

variety of molecular studies have led to the identification of certain biological markers of SDCs. Among these is HER-2, which is amplified in 20–25% of breast cancers (Moy et al., 2006; Press et al., 1997). Various studies of HER-2 in SDC have shown variable results, with amplification occurring in 25–100% of tumors (Jaspers et al., 2011). Nonetheless, the proportion is much higher than that observed in the other histological subtypes, such as the ACCs and MECs described above (Etges et al., 2003; Giannoni et al., 1995; Gibbons et al., 2001; Glisson et al., 2004; Hellquist et al., 1994; Jaehne et al., 2005; Locati et al., 2009; Milanoet al., 2007; Nguyen et al., 2003; Press et al., 1994; Skalova et al., 2001; Williams et al., 2007). HER-2 expression is considered to correlate with histological grade in both salivary gland neoplasms as well as breast cancer, and represents a potential attractive therapeutic approach for SDCs. Since HER-2 can also enhance AR function, anti-androgen therapy may be effective against MSGTs when HER-2 is overexpressed.

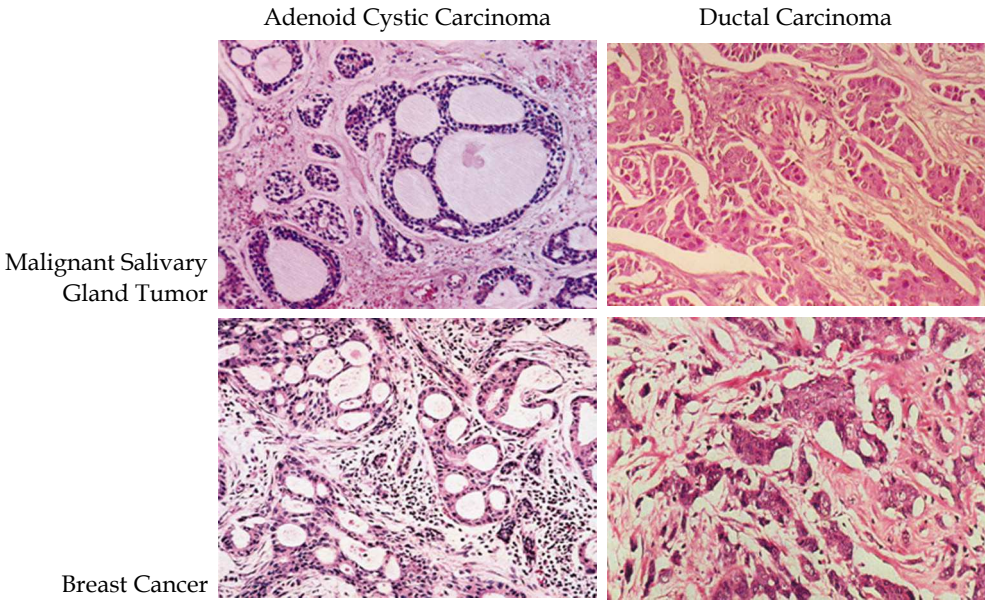
Previous studies have shown that high EGFR expression in SDCs may contribute to tumor growth (Fan et al., 2001; Locati et al., 2009). EGFR has also been shown to enhance tumorigenesis in several human carcinomas by blocking apoptosis and promoting angiogenesis (Kari et al., 2003). An interaction between both EGFR and HER-2 and hormonal pathways has also been described. In breast and uterine cancers, treatment with anti-EGF antibodies reduces tumor proliferation induced by treatment with estradiol. Likewise, the antiestrogen ICI 164,384 reduces the effects of EGF-induced tumor proliferation (Shupnik, 2004).

Hoang et al. performed molecular studies with microsatellite markers and DNA flow cytometry to compare the biological characteristics of SDC and IDC. They found that there were similar allelic alterations on chromosomal arms 6q, 16q, 17p, and 17q, and DNA aneuploidy in both malignancies; these alterations may contribute to the aggressive behavior (Hoang et al., 2001). Recently, polysomy of chromosome 7 was detected in 25% of SDCs, and this alteration correlated with poor OS (Williams et al., 2010). This correlation was also reported in IDCs, and supports the notion that EGFR gene mutations may guide therapy (Shien et al., 2005). Taken together, gene alterations of both EGFR and HER-2 may define the molecular features of these 2 types of malignancies, and these receptors may be candidates for targeted therapy.

4. Hormone therapy for the treatment of patients with MSGTs

As described above, several types of MSGTs are morphologically and biologically similar to malignant breast cancers (Pia-Foschini et al., 2003; Wick et al., 1998) (Fig. 1). Further, the clinical significance of sex hormone receptors has been debated since White and Garcelon first described therapy with estrogen against salivary gland neoplasms in 1955 (White & Garcelon, 1955). Previous reports obtained using a low number of biopsy samples have shown conflicting results regarding the expression of sex hormone receptors, making it difficult to determine the potential benefits of hormone therapy (Barnes et al., 1994; Barrera et al., 2008; Dimery et al., 1987; Dori et al., 2000; Jeannon et al., 1999; Lamey et al., 1987; Lewis et al., 1996; Miller et al., 1994; Nasser et al., 2003; Pires et al., 2004; Shick et al., 1995). Therefore, additional studies are required in order to clarify the role of hormone receptors in MSGTs. Although several studies have examined ER and PR expression in MSGTs, there is substantial disparity in the results: the expression of ER and PR varies from 0 to 86% and 0 to 50%, respectively (Barnes et al., 1994; Barrera et al., 2008; Dimery et al., 1987; Dori et al., 2000; Jeannon et al., 1999; Lamey et al., 1987; Lewis et al., 1996; Miller et al., 1994; Nasser et

al., 2003; Pires et al., 2004; Shick et al., 1995). These disparities may be explained by differences in the antibodies used, the experimental methods of detection (e.g., Western blotting vs. immunohistochemistry), and the criteria used for ruling out false positives and negatives. It is therefore particularly critical to standardize protocols in a way similar to that described for the analysis of breast cancer tissues. Some of the differences might also result from an insufficient number of samples.



Salivary glands and mammary glands are both tubulo-acinar exocrine tissues sharing similar morphological features. It is therefore expected that the tumors originating from these two different glands would show similarities in their response to hormonal treatment.

Fig. 1. Histological comparison of malignant salivary and mammary gland tumors.

Even though ER expression is unlikely to represent a useful marker for detecting MSGTs, a subset of MSGTs clearly expresses hormone receptors, and these receptors could control disease progression. Thus, current therapeutic strategies in breast cancer patients may also be effective for the treatment of MSGTs. Moreover, the feasibility of hormone therapy seems to be supported by accumulating reports of AR expression in SDCs. Although the expression of AR is generally rare in salivary gland neoplasms, SDCs commonly express AR in 92–100% of cases (Fan et al., 2001; Kapadia et al., 1998; Moriki et al., 2001). Recently, Jaspers et al. reported that androgen deprivation therapy (ADT) in patients with recurrent or disseminated disease showed a clinical benefit in 5 out of 10 cases, and 2 of these had partial responses (Jaspers et al., 2011). This approach is therefore more effective than the results obtained with chemotherapy. Given the fact that ADT generally has less adverse effects than chemotherapy, anti-androgen therapy may lead to better clinical outcomes and could become a standard treatment for SDCs.

Williams et al. reported that most tumors derived from breast and salivary glands expressed estrogen receptor-beta (ER-β) and that the patients whose tumors lacked ER-β were at higher risk for local recurrence (Williams et al., 2007). In addition, previous studies have linked the loss of ER expression to aggressive features in adenocarcinomas of the breast, prostate, and colon (Foley et al., 2000; Fuqua et al., 2003; Leygue et al., 1999; Maggiolini et al., 2004; Strom et al., 2004; Wong et al., 2005). In breast and prostate carcinoma, ER-β has been shown to inhibit cell proliferation via the cyclin D1 pathway, and to induce apoptosis by downregulating bcl-2 and/or by inducing Bax expression (Bardin et al., 2004; Pettersson et al., 2000). Targeting ER-β may therefore become a useful approach for the management of salivary duct carcinoma.

In our previous studies, we determined that MSGT cell lines in culture lacked estrogen and progesterone receptors. However, the lack of hormone receptors may be a consequence of malignant transformation and may represent a requirement for the establishment of immortal cell lines. Other clinical studies have reported the efficacy of Tamoxifen against MSGTs (Elkin & Jacobs, 2008; Shadaba et al., 1997), and one resulted in long-term survival even though in these patients, no ER was detected by immunohistochemistry. This result appears to be supported by another case report where Tamoxifen could reactivate ER expression (Sharma et al., 2006). Our previous studies showed that progesterone could suppress MGST cell aggressiveness in a manner similar to that observed in breast cancer cells (Fig. 2). Specifically, we demonstrated that after transduction of PR, progesterone could significantly suppress the proliferation (and invasion) of MSGT cells (Yoshimura et al., 2007). This suppression did not lead to cell death, but instead to cell cycle arrest. These data suggest that if MSGTs express significant levels of PR, then progesterone treatment may slow the growth of the primary tumor and potentially shift it to a dormant state. Since most MSGTs occur in elderly patients, triggering tumor dormancy could improve the quality of

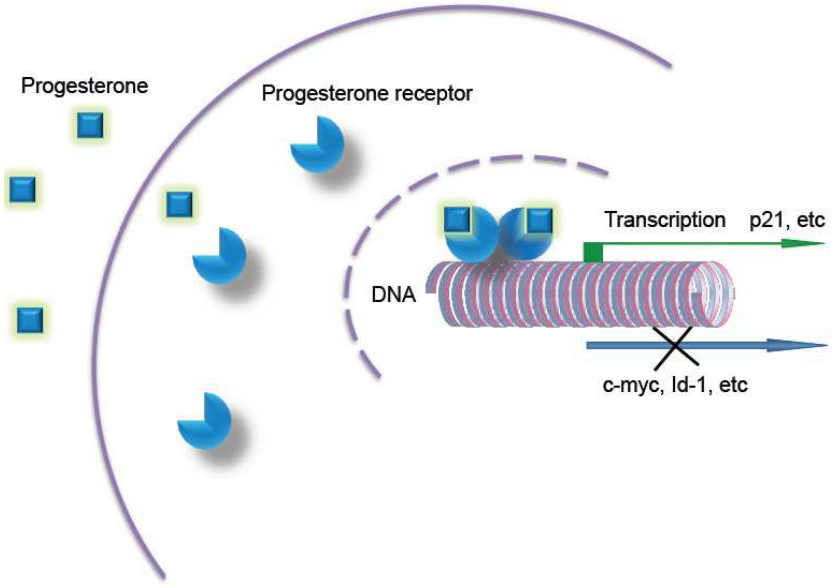


Fig. 2. Pg suppresses proliferation and invasion of both salivary gland and breast cancer cells.

life, and may be a successful way to allow the patient to live a normal lifespan. Although the 5-year OS in patients with MSGTs represents the average, extended survival rates are extremely low (Lones et al., 1997; Lopes et al., 1998; Spiro, 1997). MSGTs show low sensitivity to chemotherapy and surgery because of anatomical limitations (Marabdas et al., 1990; Takagi et al., 2001). Since radiation is also less effective, novel therapeutic approaches are eagerly anticipated. Triggering tumor dormancy as a consequence of hormone therapy could represent a novel strategy for the treatment of patients with MSGTs.

In our recent studies, the inhibitory effect of Pg on the proliferative and invasive activities of the salivary gland and breast tumor cells was demonstrated, suggesting some common mechanisms. In both types of cancers, expression of Id-1 and c-myc was down-regulated after Pg treatment, whereas p21 expression level was up-regulated.

5. Conclusions

Besides surgical resection and radiation of MSGTs, there are no other effective therapies. Adjuvant therapy is generally reserved for palliative treatment; however, there is no clear evidence that such treatment can bring clinical benefits. Since adverse effects caused by chemotherapy often threaten the life of a patient, and since some patients with specific MSGTs, especially ACCs, show long survival even with multiple metastases, the adoption of adjuvant therapy should be carefully considered. To achieve new therapeutic methods, it is now necessary to clarify several unanswered questions regarding the expression and/or function of sex steroid hormone receptors in MSGTs. As indicated by AR expression in SDCs, there is now evidence linking hormone receptors and growth factor receptors to the disease. Expression of these receptors could render tumors sensitive to hormone therapy. However, to improve clinical outcomes of patients with rather rare malignancies, more accurate data obtained from multiple and larger studies are required. MSGTs tend to occur in elderly patients, and triggering tumor dormancy could be a successful means of slowing disease progression, therefore providing an improvement in their quality of life. Our studies on PR-negative cells also suggest that induction of hormone receptor gene expression might be an option for delaying disease progression. Based on multiple lines of evidence from a range of cancers, sex steroid hormone receptors may prove to be appropriate targets for the establishment of novel treatments for patients with MSGTs.

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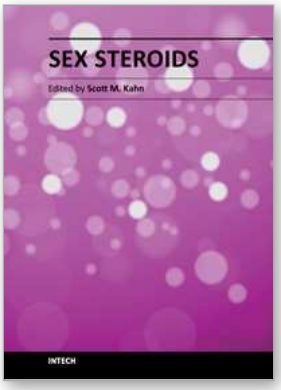

Sex Steroids

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This book, entitled "Sex Steroids", features a valuable collection of reviews and research articles written by experts in signal transduction, cellular biology, diseases and disorders. "Sex Steroids" is comprised of four sections, "The Biology of Sex Steroids", "Sex Steroids, Memory, and the Brain", "Sex Steroids and the Immune Response", and "Therapy"; individual chapters address a broad range of recognized and predicted functions and applications of sex steroids. "Sex Steroids" is intended to provide seasoned veterans as well as newcomers to this area of research with informative, resourceful, and provocative insights. Readers of "Sex Steroids" should emerge with an appreciation and understanding of the multitude and complexity of biologic processes attributed to these important hormones, and possible future directions of research in this fascinating and ever evolving field.

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