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Our goal is to understand how breast cancers become resistant to hormone treatments. Study targets are the hormones, estradiol and progesterone; their antagonists, tamoxifen and RU486; and the receptors to which they all bind, estrogen (ER) and progesterone receptors (PR). There are two PRs -- the A- and B-isoforms. We created breast cancer cell models that express one or the other PR, and find that A- is inhibitory while B- is stimulatory. We address the paradox that progestins can stimulate growth of breast cancers, yet high doses successfully inhibit breast cancers. We discovered two proteins that interact with tamoxifen-occupied receptors, and alter the direction of transcription. The coactivator L7/SPA **increases** the agonist effects of tamoxifen but not estradiol. The corepressors NCoR and SMRT **suppress** the agonist activity of tamoxifen. We postulated that L7/SPA accelerates development of hormone resistance while the corepressors retard it. We tested this in a small cohort of tumors from tamoxifen sensitive or tamoxifen resistant patients. Initial studies indicate that corepressor levels are lower in resistant tumors, as predicted. Coactivators and corepressors could become predictive markers for tamoxifen resistance, and even therapeutic targets.

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5. INTRODUCTION

The research in our laboratory focuses on breast cancer, and how the steroid hormones produced by the ovaries -- estradiol and progesterone -- are involved in the development and growth of these cancers.

Additionally, because many breast cancers are hormone-dependent, which means that their growth is enhanced by estradiol and progesterone, treatment often involves the use of drugs that interfere with the actions of these hormones. Such interfering drugs are called steroid hormone antagonists. The best known of these antagonists are the antiestrogen, tamoxifen, and the antiprogestin, RU486. We seek to understand how antagonists block the stimulatory effects of the steroid hormones in breast cancers.

In hormone responsive tumors, growth is initially retarded by antagonists, and remissions occur. This is desirable. A key problem with use of antagonists to treat breast cancers, however, is that eventually tumors acquire resistance to the antagonist and resume growing. We seek to understand how tumors acquire resistance, with the goal of trying to block this process so that the effectiveness of antagonist treatments can be prolonged. Another outcome of this work is that it may suggest methods to design and screen for better antagonists; perhaps ones against which resistance is less likely to develop.

The long-term goal is to improve the strategies and outcomes of steroid hormone therapies in breast cancers: by understanding how hormones control cancer growth; by understanding how tumors become resistant to hormone treatments; and by devising ways to predict or avoid dev elopment of resistance.

6. BODY

MECHANISMS OF STEROID HORMONE ACTION: HORMONE RECEPTORS

Estradiol and progesterone are hormonal agonists produced by the ovaries. These hormones then enter the blood stream and reach their target organs which, in addition to the breasts, include the uterus and cervix, bones, blood vessels, skin, brain and other sites. These organs are "targets" for the hormones because their cell nuclei have proteins called "hormone receptors". When the hormone reaches the target cells, it passes through the cell cytoplasm and into the nucleus, where it encounters and binds the appropriate receptors. This binding activates the receptors, which in turn bind to specific DNA sequences located in front of the genes being regulated, and (usually) activates those genes. In other words, steroid hormone receptors are transcription factors whose function is controlled by hormone binding. Breast cancers whose growth is stimulated by estradiol and/or progesterone, do so because the tumor cells have estrogen- (ER) and/or progesterone receptors (PR) which bind these hormones. Like the agonists, the antagonists tamoxifen and RU486, bind the tumor ER and PR respectively, and block the effects of the hormonal agonists at those sites; hence the term "antagonist".

The structure of nuclear steroid receptors has been partially characterized. These are large proteins with modular functional domains. At the downstream, or C-terminal end, is the hormone binding domain (HBD). A hinge region separates the HBD from a centrally positioned DNA binding domain (DBD) through which the receptors interact with DNA. Upstream of this, at the N-terminus, are transcriptional activation functions and other poorly defined domains. Both PRs and ERs have this same generic structure. There are two isoforms of PRs that differ in size: PR B-receptors have a 164 amino-acid extension at the far N-terminus (the B-upstream segment, or BUS), which is missing in PR A-receptors. Because of this, the two PR isoforms have different gene regulatory properties when they are occupied by agonists or antagonists at the HBD.

This grant was activated June 15, 1994. Publications are cited in section 8.

HIGHLIGHTS OF PROGRESS

Demonstration of PR exon splice variants in breast cancers. Because of the functional differences between PR A- and B-receptors, we undertook an analysis of the PR isoform distribution in breast cancer cell lines and clinical tumor specimens. RT- PCR was used to analyze PR transcripts, and immunoblotting to analyze PR proteins. We find that normal and malignant breast tissues, endometrial cancers and breast cancer cell lines, express unequal amounts of wild-type B- and A-receptors, plus anomalous forms of PR. PR are encoded by transcripts assembled from 8 exons. We isolated four variants that contain precise deletions of exons encoding the DBD or HBD. The transcripts lack exon 2 (PR 2), exon 4 (PR 4), exon 6 (PR 6) or exons 5 and 6 (PRΔ 5,6). They encode receptors truncated upstream of the DBD (Δ2); missing the proximal or central region of the HBD (4, 5,6); or truncated in the center of the HBD (Δ6). The Δ4 variant is also found in the normal breast tissue adjoining a tumor. Two variants, AΔ6 and AΔ5,6 cloned into the background of the PR A-isoform, comigrate with similar proteins present on immunoblots of breast tumor extracts. AΔ6 binds DNA constitutively while AΔ5,6 does not bind DNA *in vitro*. Nevertheless, both variants are dominant-negative transcriptional inhibitors of wild-type A- and B-receptors. **It is possible that expression of variant PRs can compromise the accuracy of receptor measurements as markers of hormone-dependent cancers, and perhaps modify the responses of tumors to progestin therapies.** *Richer JK et al. Breast Cancer Research and Treatment, 48:231, 1998.*

RU486-occupied B-receptors are transcriptional agonists. When antagonists have agonist-like effects, the clinical consequences are grave. This study first reported that RU-486-occupied B- but not A-receptors, inappropriately activate transcription. Moreover, on a complex promoter, transcription did not require PR binding to DNA. On the complex thymidine kinase promoter (PRE-*tk*-CAT) B-receptors strongly activated CAT transcription with the agonist R5020, and with three antiprogestins: RU486, ZK112993 (mixed antagonists), and ZK98299 (pure antagonist). Since ZK98299-occuped B-receptors do not bind DNA, the data suggested that transcription from the *tk* promoter occurs did not require the PRE. Indeed, *tk*-CAT lacking the PRE loses responsivenes to the agonist, but the three antagonists still activate CAT transcription.

The PRE-independent, antagonist-induced transcription requires that PR have an intact DNA binding domain, but PR target gene specificity is not required, because a PR mutant that binds an estrogen response element also activates transcription. Thus antagonist-occupied PR can activate transcription without binding DNA directly, perhaps by interacting with tethering proteins (see confirmation of this using the p21 promoter, below). This suggests that even a gene that is not a normal progesterone target could be aberrantly activated by antiprogestins. Unlike B-receptors, A-receptors are not activated by antiprogestins and, when the two isoforms are coexpressed, A-receptors annul the inappropriate transcription by B-receptors. Thus, when both receptor isoforms are present, the inhibitory A-receptor phenotype is dominant. These studies suggest that the two PR isoforms are functionally different, and that the agonist-like transcriptional effects of antagonist-occupied B-receptors can proceed through novel DNA binding independent mechanisms. *Tung L et al. Molec Endocrinol 7:1256, 1993.*

A-receptors inhibit B-receptors in the A/B heterodimer: Novel method to generate pure heterodimers. When transfected separately, each PR isoform exhibits different transcriptional properties that are ligand- and promoter-specific. However, the two receptor isoforms coexist in target tissues, so that a mixture of three dimeric species, A:A, A:B and B:B, bind to DNA and regulate transcription. Under normal conditions, it is impossible to study the transcriptional phenotype of pure A:B heterodimers uncontaminated by the homodimers. In order to study A:B heterodimers in isolation, we exploited the property of the 40 amino-acid leucine zipper (zip) domains of fos and jun, to form pure PR heterodimers. Chimeric constructs were made linking the zip of either c-fos or c-jun to the C-terminus of B- or A-receptors (PR-zip) to produce A-fos, B-fos, A-jun or B-jun. To determine which PR isoform is functionally dominant in the A:B heterodimer, cells expressing A- plus B-zip chimeras were treated with RU486, which produces opposite transcriptional effects with each isoform. Gel mobility shift and immune coprecipitation assays show that in the presence of RU486, only pure heterodimers form between A-fos:B-jun or A-jun:B-fos, and bind DNA at PREs. Under these conditions, RU-486-occupied B-zip homodimers stimulate transcription, RU-486-occupied A-zip homodimers are inhibitory, and pure A:B zip heterodimers have the inhibitory phenotype of the A-zip homodimers. We conclude that, in heterodimers, A-receptors are dominant-negative inhibitors of their B-receptor partners. Interestingly, the pure PR-zip heterodimers, unlike wild-type receptors, bind a PRE in the absence of hormone. However, they do not activate transcription. Thus, PR dimerization and PRE binding are necessary, but without hormone, are insufficient to activate transcription. *Mohamed MK et al. J Steroid Biochem Molec Biol 51:241, 1994.*

cAMP switches RU486 to an agonist in wild-type T47D cells that contain both B- and A-receptors. This paper shows that antiprogestin-occupied wild-type PR can generate an apparent PR-resistant phenotype through cross-talk with cAMP signaling pathways. Because antiprogestins are growth inhibitors in experimental mammary cancers, they are in Phase III clinical trials for the treatment of breast cancer. However, we find that when cellular cAMP levels are elevated, antiprogestins can, inappropriately, activate

transcription. In breast cancer cells that naturally coexpress B- and A-receptors and a stably transfected MMTV promoter-CAT reporter, the mixed antagonists RU486 and ZK112993 are transcriptionally inactive and suppress the effects of progesterone. However, the mixed antagonists become strong activators in the presence of cAMP. This functional switch does not occur with the pure antagonist ZK98299. **It is possible that hormone "resistance" results from such unintended stimulation of breast cancers by mixed antagonists like RU486 or tamoxifen**. *Sartorius CA et al. J Biol Chem 268:9262, 1993.*

Only RU486-occupied B-receptors are activated by cAMP. Since the two PR isoforms have dissimilar effects on agonist-mediated transcription, we studied transcription by antiprogestins and cAMP on each PR isoform separately, using transiently expressed receptors. The results show that antiprogestin-occupied B-receptors but not A-receptors become transcriptional activators in the presence of cAMP. *Sartorius CA et al.* Cancer Research 54:3868, 1994.

How do B-receptors differ from A-receptors? A third activation function, AF3, in BUS. We postulated that BUS is in part responsible for the functional differences between the two isoforms, and constructed a series of PR expression vectors encoding BUS fused to isolated downstream functional domains. These constructs include BUS, linked to the DBD or to each of the two transactivation domains, AF1 and AF2. BUS-DBD-NLS binds tightly to DNA aided by accessory nuclear factors. In HeLa cells, it strongly and autonomously activates transcription. Transcription levels with BUS-DBD-NLS are equivalent to those seen with full-length B-receptors, and are 10-fold higher than those seen with A-receptors. BUS specifically requires an intact steroid receptor DBD. PR DBD mutants that cannot bind DNA, or the GAL 4 DBD, cannot cooperate in BUS transcriptional activity. However, strong transcription by BUS-DBD-NLS is promoter- and cell-specific. It lacks autonomous activity in T47D-Y cells (see below), but BUS-DBD-NLS-regulated transcription can be reconstituted by elevating cellular levels of cAMP or by linking BUS to AF1 or AF2, each of which alone is also inactive in these cells. We conclude that B-receptors contain a unique third AF3 located in BUS and requiring a functional PR DBD. Depending on the promoter or cell, AF3 can activate transcription autonomously, or it can functionally synergize with AF1 or AF2. **This is the first demonstration of a third activation function in any steroid receptor**. *Sartorius CA et al. Molec Endocrinol 8:1347, 1994.*

A novel inhibitory function, IF, operates only in the context of A-receptors. While analyzing cooperativity among the three Afs, we discovered a novel inhibitory function (IF) that represses transcription only in the context of A-receptors. The strong transcriptional activity of B-receptors is due, in part, to synergy produced by cooperativity between AF3, and one of the two downstream Afs. Additionally, we find that the proximal N-terminus of PR common to both isoforms contains an IF located in the 292 amino acid segment lying between AF3 and AF1. Removal of IF increases the

transcriptional activity of A-receptors 10 fold; to the levels of B-receptors. While IF suppresses the activity of A-receptors, it is not inhibitory in the context of B-receptors. We speculate that BUS constrains the repressor function of IF. As a result, IF inhibits AF1 or AF2, but not AF3. The inhibitory function of IF is transferable to ER. We postulate that IF mediates the dominant-negative effects of A-receptors on its B-receptor partner in the A:B heterodimer and on transcription by ER (see below), perhaps through recruitment of a repressor. These data demonstrate the existence of a novel inhibitory function in PR which, together with the three Afs, accounts in part for the complex transcriptional repertoire of these receptors. Furthermore, mapping of IF to the N-terminus begins to assign novel functions to this large, relatively undefined, structural region of human PR. *Hovland AR et al. J Biol Chem. 273:5455, 1998.*

PR Phosphorylation. PR are extensively phosphorylated but the function of this covalent modification is unknown. To study the role of phosphorylation on the unique properties of A- *vs.* B-receptors we constructed and tested four sets of serine to alanine substitution mutants: ten serine clusters, located in regions common to both PR isoforms (the M-series mutants) were mutated in **1)** A-receptors and **2)** B-receptors. Six serine clusters located in the 164 kDa BUS segment (the B-series mutants) were mutated individually and collectively and cloned into **3)** B-receptors and **4)** into BUS-DBD-NLS, a constitutive transactivator, in which the AF3 function of BUS is fused to the PR DBD-NLS. Transcription by most of the M-series mutants resembles that of wild-type A- or B-receptors. Mutation of three sites – Ser^{190} at the N-terminus of A-receptors; a cluster of serines upstream of the DBD; or Ser^{676} in the hinge – inhibits transcription by 20-50% depending on cell or promoter context. These sites lie outside AF1 or AF2. M-series mutants remain substrates for a hormone-dependent phosphorylation step and they all bind well to DNA. Progressive mutation of the B-series clusters leads to the gradual dephosphorylation of BUS, but only the six-site mutant, involving ten serine residues, is completely dephosphorylated. These data suggest that in BUS, alternate serines are phosphorylated or dephosphorylated at any time. However, even when BUS is completely dephosphorylated, both BUS-DBD-NLS and full-length B-receptors remain strong transactivators. We conclude that differential phosphorylation does not explain the transcriptional differences between the two PR isoforms. *Takimoto GS et al. J Biol Chem 271:13308, 1996.*

Many nuclear receptors undergo ligand-dependent down-regulation. This may be an important mechanism for a) controlling the levels of steroid receptors; and b) controlling the length of time by which a steroid hormones signal the transcriptional apparatus. c) ER and PR levels in breast cancers are the major markers by which hormone responsiveness can be predicted, and their loss is associated with steroid hormone resistance. We have now discovered one mechanism by which PR levels are regulated. We find that in breast cancer cells, PR are ubuiquitinated and degraded by the 26S proteasome. They are targeted for ubiquitination by MAPK (mitogen activated protein kinase) phosphoprylation. In addition to mitogens, we find that progestins activate p42/44 MAPKs. Inhibitors of MAPK activation (MEK inhibitors), block the ligand-dependent

degradation of PRs. Mutation of a specific MAPK-consensus phosphorylation site on PR – Ser^{294} – completely stabilizes the receptors in the presence of ligand. **These data are the first to demonstrate a specific function for phosphorylation, and reveal a direct mechanism for cross-talk between PR and MAPK signaling** (see also below). *Lange et al. 1999, submitted.*

RU486-occupied A-receptors are dominant-negative inhibitors of ER. Phosphorylation deficient B-receptors do not acquire the ER inhibitory properties of RU486-occupied A-receptors, and unlike A-receptors, they retain the ability to activate transcription in synergy with cAMP and antiprogestins. We conclude that phosphorylation has only subtle effects on the complex transcriptional repertoire that distinguishes the two PR isoforms. It does not influence transcription mediated by AF1, AF2 or AF3; it is not responsible for the unusual ability of antiprogestin-occupied A-receptors to repress ER; or of RU486-occupied B-receptors to activate transcription through cross-talk with cAMP. *Takimoto GS et al. J Biol Chem 271:13308, 1996.*

Mechanisms: transcriptional coregulators switch antagonists to transcriptional agonists. We speculated that the mechanisms by which antagonist-occupied receptors become agonists, involve recruitment of coactivators to the transcription complex. A yeast two-hybrid screen was used to isolate such factors. A LexA DNA binding domain-PR H-HBD fusion protein was screened against a HeLa cell expression library using yeast cells treated with RU486. Several cDNAs were isolated, two of which are of particular interest with respect to the stimulatory *vs.* inhibitory actions of antiprogestins and antiestrogens: one encodes a 27 kDa human protein that has a bZIP motif and a zinc finger DNA binding domain. When this protein (termed L7/SPA: "switch protein for antagonists") is coexpressed with RU486-occupied PR or tamoxifen-occupied ER it enhances the agonist activity of these antagonists. Thus, recruitment of SPA or related coactivators to antagonist-occupied receptors can account for their inappropriate agonist-like activity. A second cDNA was the human homolog of the mouse retinoic acid/thyroid receptor corepressor (mN-CoR) interaction domain (ID) (28-30). Full-length 7500bp human N-CoR was cloned and sequenced.The isolation of N-CoR was surprising, since it does not bind unliganded or agonist-liganded steroid receptors. However, we show that N-CoR binds antagonist-occupied steroid receptors. **This suggests that antagonists adventitiously recruit to DNA, repressors that do not normally function in steroid hormone action. If so, antagonist-occupied receptors are not simply transcriptionally silent, but can actively inhibit transcription.**

Overexpression of N-CoR, or the related corepressor, SMRT, suppresses the agonist activity of RU486-occupied PR and tamoxifen-occupied ER, and this inhibitory activity can be squelched by an ER or PR HBD. **We propose that the continuum of steroid hormone antagonist activity, ranging from complete inhibition on the one hand, to strong agonist-like activity on the other, is controlled by the ratio of coactivators to corepressors bound to receptors. Observations that tamoxifen is an antagonist in the**

breast but an agonist in the uterus, could be explained by a model in which the stoichiometry of receptor-bound coregulators shifts from an excess of corepressors to an excess of coactivators in different tissues. Similarly, in breast cancers, underproduction of corepressors, or overproduction of coactivators associated with tumor progression, could explain the tendency of tamoxifen-sensitive tumors to convert to tamoxifen-resistant states. *Jackson TA et al. Molec. Endocr. 11:693, 1997.*

Construction of breast cancer cell lines for the independent study of PR A- *vs.* B-receptors. We developed model cell lines to study each PR isoform independently plus PR-negative controls, in a stable breast cancer setting under conditions in which estrogen priming of PR is not required: First, (*a*) a stable PR-negative monoclonal subline (T47D-Y) of PR-positive, estrogen-resistant T47DCO breast cancer cells was selected by flow-cytometric PR screening. T47D-Y cells are PR-negative by immunoassays; by ligand binding assay; by growth resistance to progestins; by failure of extracts to bind a PRE *in vitro*; and by failure to transactivate transfected PRE-regulated promoters *in vivo*. Then, (*b*) T47D-Y cells were stably transfected with expression vectors encoding one or the other PR isoform, and two monoclonal cell lines were selected that express either B-receptors (T47D-YB) or A-receptors (T47D-YA) at levels equal to those seen in natural T47D cells. The ectopically expressed receptors are properly phosphorylated, and like endogenously expressed receptors, they undergo ligand-dependent down-regulation. The expected B:B or A:A homodimers are present in cell extracts from each cell line but A:B heterodimers are missing in both. **These cells are the only model for the independent study of human B- *vs.* A-receptors; we have filled requests for them world-wide.** *Sartorius CA, et al. Cancer Research 54:1347, 1994.*

Cell lines: only antiprogestin-occupied B-receptors are activated by cAMP. These cells were used to study isoform-specific transcriptional effects of antagonists. With agonists, cAMP-dependent transcriptional synergism of PRE-regulated promoters is seen in both A- and B-receptor-expressing cell lines. However, the mixed antiprogestins RU486 or ZK112993, have agonist-like activity only in YB cells. Pure antiprogestins like ZK98299, lack agonist activity in both cell lines. *Sartorius CA, et al. Cancer Res 54:3868, 1994.*

The new cell lines allow the study of progestational effects without estradiol priming of PR. The confounding effects of estrogens hinders study of progestins in all other cell lines. These cells also allow the study of long-term progestin effects, such as growth, as mediated by each isoform independently. We have stably inserted PRE-CAT reporters into each cell line (not shown) so that PR-dependent transcriptional effects can be studied in parallel with proliferative effects in the same endocrine setting. For example, as shown in *Groshong et al.*, cells growth-arrested by one pulse of progesterone, cannot resume growing after a second progesterone pulse, yet the second progesterone pulse activates CAT transcription. Thus, the growth arrest is not due to failure of PR signaling.

Progesterone has biphasic effects, first stimulating, then inhibiting growth. Depending on the tissue, progesterone is classified as a proliferative or a differentiative hormone. These opposing views are currently reflected in clinical practice. For example, progestins are added to estrogens for hormone replacement therapy at menopause, because they block the proliferative and tumorigenic effects of unopposed estrogens in the uterus. However, women who have been hysterectomized are not given progestins to spare their breasts from the proliferative effects of these hormones. This is defended by the prevailing notion that progesterone is differentiative in the uterus but proliferative in the breast. To explain this paradox, we studied progestin-regulated growth in YB breast cancer cells. A pulse of progesterone accelerates cells through the first mitotic cell cycle, but arrests them in late G1 of the second cell cycle. A second dose of progesterone cannot restart cell growth despite adequate levels of transcriptionally competent PR. The acquired progesterone resistance is accompanied by decreased levels of cyclins D1, D3 and E, disappearance of cyclins A and B, and sequential induction of the cdk inhibitor p21 followed by p27. The retinoblastoma protein product is hypophosphorylated and extensively down-regulated. The second progesterone dose prolongs p21 upregulation and p27 levels rise even higher, thereby intensifying the growth inhibition through an autoinhibitory loop. *Groshong SD et al. Molec. Endocr. 11:1593, 1997.*

Progesterone and EGF cross-talk: A pulse of progesterone primes cells for the proliferative effects of EGF but continuous progesterone inhibits growth: Does this explain how progesterone can be either proliferative or differentiative? Despite resistance to a second pulse of progesterone, the cell cycling machinery is poised to restart. Naive T47D-YB cells are resistant to the proliferative effects of EGF. However, the first dose of progesterone reverses the EGF-resistance and transiently sensitizes cells to the proliferative effects of EGF, during a narrow window of opportunity created as p21 levels fall and before p27 levels peak. These data suggest the concept that progesterone is neither inherently proliferative nor antiproliferative, but that it regulates a cell-cycle restriction point upon which other growth factors influence the fate of the cell. Another surprising finding is that the proliferative resistance to progesterone is not at the level of PR signaling. In fact, the growth arrest appears to require the presence of functional PR since it is due to sustained upregulation of p21 and p27, produced via a positive feed-back loop initiated by two sequential progesterone treatments. **Thus, we postulate that sustained progesterone is autoinhibitory, while transient or cyclical progesterone is growth stimulatory; i.e progesterone can either suppress or accelerate growth depending on the regimen. This has implications for contraception, hormone replacement therapy or cancer treatment regimens, since it predicts that the effects of continuously administered progestins differ significantly from those of episodically or cyclically administered progestins; the former would be growth inhibitory and the latter stimulatory. This model may explain why high-dose, continuous progestin therapy inhibits growth of breast cancers, while physiological and cyclic progestins are proliferative in the breast. A model in which the rate and duration of progesterone treatment controls the type of response would reconcile contradictory views that this hormone is either proliferative or differentiative.** *Groshong SD et al. Molec. Endocr. 11:1593, 1997.*

Growth control by PR: Progesterone regulates transcription of the p21 gene through Sp1 and CBP/p300. The biphasic effects of progesterone on growth of breast cancer cells is accompanied by upregulation of the cyclin-dependent kinase inhibitor, p21. To understand how progesterone influences this important cell-cycle regulatory protein, we studied transcription of the p21 promoter. We find that progesterone regulates transcription of the p21 promoter by an unusual mechanism. This promoter lacks a canonical PRE. Instead, PRs bind the promoter by being tethered to the transcription factor Sp1, at the third and fourth of six Sp1 binding sites located just upstream of the TATA box. Mutation of Sp1 site 3 eliminates basal transcription, and mutation of sites 3 and 4 eliminates transcriptional upregulation by progesterone. Progesterone-mediated transcription is also prevented by overexpression of E1A, suggesting that CBP/p300 is required. Indeed, in HeLa cells, Sp1 and CBP/p300 associate with stably integrated *flag*-tagged PR in a multiprotein complex. Since many signals converge on p21, cross-talk between PR and other factors colocalized on the p21 promoter may explain how progesterone can be proliferative or differentiative in different target cells. *Owen GI et al. Journal Biol Chem 2273:10696, 1998.*

Convergence of progesterone and EGF signaling in breast cancer. Potentiation of MAPK pathways. During late stages of breast cancer progression, tumors acquire steroid hormone resistance with concurrent amplification of growth factor receptors; this alteration predicts a poor prognosis. Since progesterone pretreatment of breast cancer cells sensitizes them to the proliferative effects of EGF, we undertook a study of the mechanisms involved in cross-talk between progesterone and EGF signaling. We find that following treatment with R5020, breast cancer cells undergo a "biochemical shift" in the regulation of EGF-stimulated signaling pathways: R5020 potentiates the effects of EGF by upregulating EGFR, c-erbB2 and c-erbB3 receptors, and by enhancing EGF-stimulated tyrosine-phosphorylation of signaling molecules known to associate with activated type I receptors. Independently of EGF, R5020 alone increases Stat5 protein levels, the association of Stat5 with phosphotyrosine-containing proteins, and tyrosine phosphorylation of JAK2 and Shc. Furthermore, progestins "prime" breast cancer cells for growth signals by potentiating EGF-stimulated p42/p44 MAP kinase, p38 MAP kinase, and JNK activities. Although the levels of Cyclin D1, cyclin E, and the CDK-inhibitor p21, are upregulated by R5020 alone, they are synergistically upregulated by EGF in the presence of R5020. Upregulation of cell cycle proteins by EGF is blocked by inhibition of p42/p44 MAPK only in the presence of R5020, supporting a shift in the regulation of these cell cycle mediators from MAPK-independent to MAPK-dependent pathways. In summary, progesterone selectively increases the sensitivity of key kinase cascades to growth factors, thereby priming cells for stimulation by latent growth signals. **These data support a model in which breast cancer cell growth switches from steroid hormone to growth factor-dependence.** *Lange CA et al. J Biol Chem,* 273: 31308, *1998.*

Convergence of progesterone with growth factor and cytokine signaling. PR regulate Stat5 expression and activity. These studies pointed to STATs as signaling intermediates

whose activity was altered by progesterone. STATs are latent transcription factors activated in the cytoplasm by diverse cell surface signaling molecules. STATs are required for normal mammary gland growth and differentiation. Their levels are upregulated during pregnancy, a period dominated by progesterone. We showed that EGF only activates Stat5 **after** progesterone pretreatment.Additionally, progestins upregulate Stat5 and Stat3 protein levels in a PR-dependent manner. Additionally, progestins induce the association of Stat5 with JAK2, a tyrosine kinase that phosporylates STATs. Further, progestin treatment induces translocation of Stat5 into the nucleus, possibly mediated by physical interaction between PR and Stat5. Progestin pretreatment of breast cancer cells is required to enable prolactin to stimulate the transcriptional activity of Stat5 on a β-casein promoter, and progesterone synergizes with EGF to control transcription of the p21 and *c-fos* promoters. **These data suggest a novel, cytoplasmic site, for the convergence of progesterone and growth factor/cytokine signaling pathways, and suggest mechanisms for coordination of proliferative and differentiative events in the breast.** *Richer JK et al. J Biol Chem,* 273:31317, *1998.*

Mechanisms underlying growth regulation by progestins, and convergence of growth factor and steroid hormone signaling are reviewed in *Lange CA, et al. Molecular Endocrinology 13:829, 1999.*

One goal of our research is to understand, and perhaps develop mechanisms for predicting, which breast tumors will acquire resistance to tamoxifen treatment. In light of our discovery that the activity of the steroid antagonists RU486 and tamoxifen can be controlled by recruitement of coactivators and corepressors. Coactivators enhance the agonist-like effects of tamoxifen; corepressors enhance its inhibitory effects.

Resistance to tamoxifen is a poorly understood and critical issue in breast cancer treatment. We hypothesized that resistance to tamoxifen is the result of increased agonist activity of this mixed antagonist. We postulated that expression levels of transcriptional coregulators may be important determinants of tamoxifen response – namely that overexpression of coactivators enhance the agonist effects of tamoxifen, and that corepressors suppress its transcriptional activity. We developed a sensitive, quantitative RT-PCR strategy to measure the levels of two corepressors (N-CoR and SMRT) and two coactivators (L7/SPA and SRC-1) in cell lines and breast tumors from tamoxifen sensitive and resistant patients. All transcripts were quantifiable in total RNA from a panel of cell lines and breast tumors. SMRT was expressed as three isoforms: the previously described full length and Δ1330-1375 splice variant forms, and a novel Δ1300-1375 alternatively spliced form. All three isoforms repress tamoxifen-occupied estrogen receptors in transcriptional studies. Corepressor levels were measured in a cohort of 23 tamoxifen sensitive and resistant breast tumors. There was a trend towards decreased expression of both corepressors in tamoxifen resistant tumors compared to the tamoxifen sensitive group. Coactivator levels were unchanged. These results suggest that reduction in the levels of corepressors may be involved in the development of tamoxifen resistance, and that measurement of coregulator transcripts in breast tumors may be a useful tool in the long-term management of breast cancer. *Graham et al. submitted, 1999.*

If these data are confirmed by analysis of larger numbers of tumors, corepressors may become useful therapeutic targets to prevent or reverse tamoxifen resistance.

7. KEY RESEARCH ACCOMPLISHMENTS

- ✓ Demonstration of PR splice variants in breast cancers
- ✓ Only PR B-receptors are transactivated by antiprogestins; A-receptors are transcriptional repressors
- ✓ New breast cancer cell lines were constructed that allow independent study of PR-A *vs*. B-receptors
- ✓ PR levels, and ligand dependent PR downregulation, are regulated by phosphorylation of Ser 294 which targets receptors for ubiquitination and 26S proteasome degradation
- ✓ Tamoxifen-occupied receptors recruit specific coactivators that enhance the agonist effects of the antagonist, or corepressors that make tamoxifen a better inhibitor
- ✓ Progesterone has biphasic effects on growth of breast cancer cells. Depending on the dose and schedule of treatment, the hormone can be either growth stimulatory or inhibitory
- ✓ There is important cross-talk between progesterone and growth factor signaling. Progesterone sensitizes cells to the proliferative effects of EGF by, among other things, activating STATs, the EGF signaling molecules
- ✓ In a selected set of patients whose tumors are tamoxifen responsive or resistant, a decrease in the levels of the corepressors N-CoR and SMRT is associated with resistance

8. REPORTABLE OUTCOMES

Manuscripts published during the granting period are listed below. Those marked with and asterisk are detailed above. The research also led to multiple presentations at national and international meetings by Dr. Horwitz. Her trainees, supported by this grant, submitted abstracts and presented their work at several important national meetings. Also as a result of this work new cell lines were developed that have been given to numerous investigators.

*Sartorius CA, Groshong SD, Miller LA, Powell RL, Tung L, Takimoto GS and **Horwitz KB**. New T47D breast cancer cell lines for the independent study of progesterone B- and A-receptors: only antiprogestin-occupied B-receptors are switched to transcriptional agonists by cAMP. CANCER RESEARCH, 54:3868-3877, 1994.

*Sartorius CA, Melville MY, Hovland AR, Tung L, Takimoto GS and **Horwitz KB**. A third transactivation function (AF3) in human progesterone receptors located on the unique N-terminal segment of the B-isoform. MOLEC ENDOCRINOL 8:1347-1360, 1994.

*Mohamed MK, Tung L, Takimoto GS and **Horwitz KB**. The leucine zippers of c-Fos and c-Jun for progesterone receptor dimerization: A-dominance in the A/B heterodimer. J STEROID BIOCH MOL BIOL 51:241-250, 1994.

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Takimoto GS, Hovland AR, Tasset DM, Melville MY, Tung L and **Horwitz KB**. Role of phosphorylation on DNA binding and transcriptional functions of human progesterone receptors. J BIOL CHEM 271:13308-13316, 1996.

***Horwitz KB**, Jackson TA, Bain DL, Richer JK, Takimoto GS and Tung L. Nuclear receptor coactivators and corepressors. MOLEC ENDOCRINOL 10:1167-1177, 1996.

*Jackson TA, Richer JK, Bain DL, Takimoto GS, Tung L and **Horwitz KB**. The partial agonist activity of antagonist-occupied steroid receptors is controlled by a novel hinge-domain binding coactivator, L7/SPA and the corepressors N-CoR or SMRT. MOLEC ENDOCRINOL 11:693-705, 1997.

Petz LN, Nardulli AM, Kim J, **Horwitz KB**, Freedman LP and Shapiro DJ. DNA bending is induced by binding of the glucocorticoid receptor DNA binding domain and progesterone receptors to their response element. J STER BIOCHEM MOL BIO 60:31-41, 1997.

Miller MM, James RA, Richer JK, Gordon DF, Wood WM and **Horwitz KB**. Progesterone receptor expression of flavin-containing monooxygenase 5 is controlled by the B-isoform of progesterone receptors: Implications for tamoxifen carcinogenicity. J CLIN ENDOCR METAB 82:2956-2961, 1997.

*Groshong SD, Owen GI, Grimison B, Schauer IE, Daly MC, Langan TA, Sclafani RA, Lange CA and **Horwitz KB**. Biphasic regulation of breast cancer cell growth by progesterone: Role of the cdk inhibitors p21 and $p27^{Kip1}$. MOLEC ENDOCRINOL 11:1593-1607, 1997.

Leslie KK, Kumar NS, Richer JK, Owen GI, Takimoto GS, **Horwitz KB** and Lange C. Differential expression of the A and B isoforms of progesterone receptors in human endometrial cancer cells. ANN NY ACAD SCI, 827:17-26, 1997.

*Takimoto GS, Graham JD, Jackson TA, Tung L, Powell R, Horwitz LD and **Horwitz KB**. Tamoxifen resistant breast cancer: Coregulators determine the direction of transcription by antagonist-occupied steroid receptors. J STEROID BIOCH MOL BIO 1998, in press.

*Richer JK, Lange-Carter C, Wierman AM, Brooks KM, Jackson TA, Tung L, Takimoto GS and **Horwitz KB**. Novel progesterone receptor variants in breast cancers and normal breast cells repress transcription by wild-type receptors. BREAST CANCER RES AND TREAT 48:231-241, 1998.

*Hovland AR, Powell RL, Takimoto GS, Tung L and **Horwitz KB**. An N-terminal inhibitory function (IF) suppresses transcription by the A-isoform but not the B-isoform of human progesterone receptors. J BIOL CHEM, 273:5455-5460, 1998.

*Owen GI, Richer JK, Tung L, Takimoto GS, and **Horwitz KB**. Progesterone regulates transcription of the $p21^{WAF1}$ cyclin dependent kinase inhibitor gene through Sp1 and CBP/p300. J BIOL CHEM 273:10696-10701, 1998.

Kumar NS, Richer JK, Owen GI, Litman E, **Horwitz KB** and Leslie KK. Selective down-regulation of progesterone receptor isoform B in poorly differentiated human endometrial cancer cells: Implications for unopposed estrogen action. CANCER RESEARCH 58: 1860-1865, 1998.

Pahl PMB, Hodges-Garcia YK, McItesen L, Perryman MB, **Horwitz KB** and Horwitz LD. ZNF207, A novel zinc finger gene on chromosome 6. GENOMICS, 53: 410-412, 1998.

*Lange CA, Richer JK and **Horwitz KB**. Convergence of Progesterone and Epidermal Growth Factor Signaling in Breast Cancer. Potentiation of Mitogen-Acivated Protein Kinase Pathways. J BIOL CHEM, 273: 31308-31316, 1998.

*Richer JK, Lange CA, Manning NG, Owen GI, Powell R and **Horwitz KB**. Convergence of Progesterone with Growth Factor and Cytokine Signaling in Breast Cancer. Progesterone Receptors regulate STAT expression and activity. J BIOL CHEM, 273: 31317-31326, 1998.

*Lange CA, Richer JK and **Horwitz KB.** Hypothesis: Progesterone primes breast cancer cells for cross-talk with proliferative or antiproliferative signals. MOLECULAR ENDOCRINOLOGY, 13:829-836, 1999.

*Lange CA, Shen T and **Horwitz KB.** Mitogen activated protein kinase phosphorylation of serine 294 in progesterone receptors leads to their ligand-dependent downregulation by the 26S proteasome. SCIENCE, in press, 1999.

*Graham JD, Tung L, Fuqua SAW and **Horwitz KB**. Nuclear coregulator expression profiles: potential determinants of hormone resistance in breast cancer. Submitted, 1999.

9. CONCLUSIONS

These studies have generated important new reagents to study the two isoforms of PRs in breast cancer. This is important because the two receptors have different biological effects. In ongoing work using these reagents, we are using DNA microchip arrays, to define the genes that are regulated by PRs, focusing on those that are differentially regulated by A- vs. B-receptors. This may allow us to isolate beneficial (ie. growth inhibitory) from deleterious (ie. proliferative) effects of progestins, and target the beneficial ones directly.

Additionally, our studies begin to explain the progestin paradox. In the breast, unlike the uterus, progesterone is a proliferative hormone. Yet, in breast cancers, high dose progestins are excellent second line therapies for patients whose tumors responded to, but later became resistant to, tamoxifen. We show that the dose and timing of progestins, as well as their ability to activate growth factor signaling pathways, may explain their paradoxical actions.

Most importantly, we discovered that tamoxifen-bound ERs interact with transcription factors that can either suppress or enhance the agonist effects of tamoxifen. For successful breast cancer treatment, tamoxifen should be inhibitory. When tamoxifen becomes stimulatory the consequences can be lethal to the patient. We have isolated factors that can control whether tamoxifen is inhibitory or stimulatory. We have begun to analyze breast cancers that are either tamoxifen sensitive or resistant, for their levels of these factors. Preliminary data suggest that a decrease in the levels of repressors is associated with resistance to tamoxifen, as we would predict. We plan to continue these

analyses since they may provide entirely new ways to analyze development of resistance, and perhaps suggest strategies for avoiding it.

10. REFERENCES

See item 8, above

11. APPENDICES

Dr. Horwitz's CV is attached. It details a bibliography of all publications, abstracts, etc. Two-page NIH biosketches for Drs. Lange and Richer are also included.

12. BINDING

The report is stapled

13. FINAL REPORT

Dr. Horwitz's CV in the appendix, includes a bibliography. Major personnel involved in the research supported by this grant were Drs. Jennifer Richer and Carol Lange. Their two-page NIH biosketch is included in the appendix. Grtaduate students supported by this grant were Twila Jackson and Steve Groshong.

CURRICULUM VITAE

Revised, January 1999

Kathryn Bloch Horwitz

PERSONAL DATA

BORN:	Sosua, Dominican Republic US Citizen, 1958
MARRIED:	Lawrence D. Horwitz, M.D. Two children
HOME ADDRESS:	9853 East Ida Avenue Greenwood Village, Colorado 80111
OFFICE ADDRESS:	Department of Medicine/Endocrinology University of Colorado Health Sciences Center 4200 East Ninth Avenue - Box B151 Denver, Colorado 80262 Tel (303) 315-8443 Fax (303) 315-4525 e-mail <kate.horwitz@uchsc.edu>

EDUCATION

1958-1962	Barnard College Columbia University New York, New York	BA, 1962 (Zoology)
1962-1966	New York University Graduate School of Arts & Sciences New York, New York	MS, 1966 (Marine Biology)
1970-1973	The University of Texas Southwestern Medical School Dallas, Texas	PhD, 1975 (Medical Physiology)
1973-1975	The University of Texas Health Sciences Center Dallas and San Antonio, Texas	Graduate Research
1976-1978	The University of Texas Health Sciences Center San Antonio, Texas	Postdoctoral Fellow

PROFESSIONAL APPOINTMENTS

1962-1963	Research Assistant, Department of Hematology Montefiore Hospital, New York, New York
1963-1965	Teaching Fellow in Biology, New York University New York, New York
1966-1968	Physiologist, Biodynamics Branch U.S. Air Force School of Aerospace Medicine Brooks Air Force Base, Texas
1968-1970	Director of Laboratories, Department of Biological Sciences Wellesley College, Wellesley, Massachusetts
1978-1979	Instructor Department of Medicine University of Texas Health Science Center San Antonio, Texas
1979-1984	Assistant Professor Departments of Medicine, and Biochemistry, Biophysics and Genetics University of Colorado Health Sciences Center
1984-1989	Associate Professor Departments of Medicine and Pathology University of Colorado Health Sciences Center
1989-present	Professor Departments of Medicine and Pathology, The Molecular Biology Program & The Biomedical Sciences Program University of Colorado Health Sciences Center

HONORS AND AWARDS

Wilson S. Stone Memorial Award for Research,
University of Texas System, MD Anderson Hospital, Houston, 1976
National Board Award, Medical College of Pennsylvania, 1986
Research Career Development Award, National Cancer Institute, NIH, 1981 - 1986
National Foundation for Cancer Research, Researcher of the Year Award, 1990
NIH MERIT Award, 1992
UCHSC Department of Medicine, Basic Research Award, 1992

The Rhone Poulenc Rorer Lecture in honor of William L. McGuire, The Endocrine Society, 1993
The William U. Gardner Memorial Lecture, Yale University School of Medicine, 1993
The University of Helsinki Medal and Second Siltavouri Lecturer, Univ. of Helsinki, Finland, 1993
The President's Guest Lecture; The Society for Gynecologic Investigation, 1994
The University Lecture, Southwestern Medical School, University of Texas at Dallas, 1994
Who's Who in America; Who's Who in the World
The Nobel Assembly, Karolinska Research Lecture, Stockholm, Sweden, 1996
Plenary Lecturer, The Israel Endocrine Society, Tel-Aviv, 1997
William L. McGuire Memorial Lecture, San Antonio Breast Cancer Symposium, 1997
Plenary Lecturer, The Australian Society for Medical Research, Adelaide, 1997
The Bicentennial Lecture, University of Louisville, Kentucky, 1998
President, The Endocrine Society, 1998-1999

MEETINGS ORGANIZER

Keystone Symposium: Steroid/Thyroid/Retinoic Acid Receptor Family, 1996
Keystone Symposium: Nuclear Receptor Gene Family, 1998
Estrogen & Progesterone: Receptors and Ligands in the Next Millenium,
Society for Gynecological Investigation, 1999
Keystone Symposium: Nuclear Receptors, 2000
Satellite Symposium on Hormone Dependent Cancers
International Congress of Endocrinology, Australia, 2000

SOCIETY MEMBERSHIPS

American Federation for Clinical Research
The Endocrine Society
American Association for Cancer Research
Western Society for Clinical Investigation
The American Society for Cell Biology
American Society for Biochemistry and Molecular Biology

CURRENT EDITORIAL BOARDS

Editorial Board, BREAST CANCER RESEARCH AND TREATMENT, 1980-present
Corresponding Editor, THE JOURNAL OF STEROID BIOCHEMISTRY, 1986-present
Editorial Board, ENDOCRINE RELATED CANCER, 1994-present
Editorial Academy, INTERNATIONAL JOURNAL OF ONCOLOGY, 1994-present
Associate Editor, REPRODUCTIVE MEDICINE REVIEW, 1994-present
Editorial Board, MOLECULAR ENDOCRINOLOGY, 1996-present
Editorial Board, J. OF MAMMARY GLAND BIOLOGY AND NEOPLASIA, l995-present

SELECTED EXTRAMURAL COMMITTEES

The Endocrine Society

Program Committee, 1988-1990
Nominating Committee, 1989-1991
Chair, Nominating Committee, 1990
Council, 1992-1995
Vice-Chair, Research Affairs Subcommittee
Publications and Journals Steering Committees
President-Elect, 1997-1998
President, 1998-1999

American Association for Cancer Research

Program Committee, 1994-1995
State Legislative Committee, 1994-present

National Science Foundation

Cellular Physiology Study Section, 1985-1988

National Institutes of Health

Biochemical Endocrinology Study Section, 1989-1993
Reviewers Reserve, 1993-1997

The President's Cancer Panel

Special Commission on Breast Cancer, NCI, 1992-1993

The International Endocrine Society

Program Committee, 1994-1996

The International Congress on Hormonal Steroid

International Organizing Committee, 1997-present

SELECTED INTRAMURAL COMMITTEES

Secretary of the Executive Faculty, University of Colorado School of Medicine
Member, Executive Committee, 1983-1984, 1985-1986
Member, Faculty Senate, 1983-1984; 1985-1986; 1988-1990
Department of Medicine Faculty Promotions Committee (Assistant - Associate), 1984-present
Medical School Admissions Committee, 1986-1991
Medical Scientist Training Program, 1987-1992
Steering Committee, 1987-1992
Admissions Committee, 1987-1992
Molecular Biology Program
Space Selection Committee, 1988-1989
Curriculum Committee, 1988-1990
Admissions Committee, 1989-present

Director: Molecular Biology PhD Program for Clinical Fellows, 1993-present
Chancellor's Committee, Indirect Cost Recovery, 1989-1990
School of Medicine Standing Committee on Research Ethics, 1989-present
Fiscal Oversight Committee, School of Medicine, 1990-1991
Chair, Physiology Department Chair Search Committee, 1992-1993
University of Colorado Cancer Center
Program Director: Hormones and Cancer Program, 1994-1998

COMMUNITY SERVICE

Cancer League of Colorado
Scientific Advisory Board, 1986-1990
Chair, 1988-1990

OTHER ACTIVITIES AND FUNDING See appendix.

PUBLICATIONS

REFEREED JOURNAL ARTICLES

1. Green I and **(Horwitz) Bloch K**. Uptake of particulate matter within the thymus of adult and newborn mice. NATURE 200:1099-1101, 1963.

2. **Horwitz KB**, Ball RJ and Schmidt JP. Resistance to infection of mice and hamsters following short-term acceleration stress. AEROSPACE MEDICINE 41:1248-1251, 1971.

3. **Horwitz KB**, and McGuire WL. Specific progesterone receptor in human breast cancer. STEROIDS 25:497-505, 1975.

4. **Horwitz KB**, McGuire WL, Pearson OH and Segaloff A. Predicting response to endocrine therapy in human breast cancer: a hypothesis. SCIENCE 189:726-727, 1975.

5. **Horwitz KB**, Costlow ME and McGuire WL. MCF-7: A human breast cancer cell line with estrogen, androgen, progesterone, and glucocorticoid receptors. STEROIDS 26:785-795, 1975.

6. McGuire WL, **Horwitz KB**, and Chamness GC. A physiological role for estrogen and progesterone in breast cancer. J STEROID BIOCHEM 7:875-882, 1976.

7. **Horwitz KB** and McGuire WL. Progesterone and progesterone receptors in experimental breast cancer. CANCER RESEARCH 37:1733-1738, 1977.

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9. McGuire WL, **Horwitz KB**, Pearson OH and Segaloff A. Current status of estrogen and progesterone receptors in breast cancer. CANCER 39:2934-2947, 1977.

10. **Horwitz KB** and McGuire WL. Estrogen control of progesterone receptor in human breast cancer: correlation with nuclear processing of estrogen receptor. J BIOL CHEM 253:2223-2228, 1978.

11. McGuire WL, Zava DT, **Horwitz KB**, Garola RE and Chamness GC. Receptors and breast cancer: do we know it all? J STEROID BIOCHEM 9:461-466, 1978.

12. **Horwitz KB**, Koseki Y and McGuire WL. Estrogen control of progesterone receptors in human breast cancer: role of estradiol and antiestrogen. ENDOCRINOLOGY 103:1742-1751, 1978.

13. **Horwitz KB** and McGuire WL. Nuclear mechanisms of estrogen action: effects of estradiol and antiestrogen on cytoplasmic and nuclear estrogen receptors and nuclear receptor processing. J BIOL CHEM 253:8185-8191, 1978.

14. **Horwitz KB**, Zava DT, Jensen EM and McGuire WL. Human breast cancer cell lines: steroid receptor analyses. CANCER RESEARCH 38:2434-2437, 1978.

15. Zava DT, Landrum B, **Horwitz KB** and McGuire WL. Measurement of androgen receptor with [3H]methyltrienolone in systems containing both androgen and progesterone receptors. ENDOCRINOLOGY 104:1007-1012, 1979.

16. Martin PM, **Horwitz KB**, Ryan DS and McGuire WL. Phytoestrogen interaction with estrogen receptors in human breast cancer cells. ENDOCRINOLOGY 103:1860-1867, 1978.

17. **Horwitz KB** and McGuire WL. Actinomycin D prevents nuclear processing of estrogen receptors. J BIOL CHEM 253:6315-6318, 1978.

18. **Horwitz KB** and McGuire WL. Estrogen control of progesterone receptor induction in human breast cancer: Role of nuclear estrogen receptors. ADV EXP BIOL MED 117:95-110, 1979.

19. **Horwitz KB** and McGuire WL. Studies on mechanisms of estrogen and antiestrogen action in human breast cancer. RECENT RESULTS IN CANCER RESEARCH 71:45-58, 1980.

20. Edwards DP, Martin PM, **Horwitz KB** Chamness GC and McGuire WL. Estrogen receptors in human breast cancer: Subcellular compartmentalization of unfilled sites. EXPERIMENTAL CELL RES 127:197-213, 1980.

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25. **Horwitz KB**, Mockus MB and Lessey BA. Variant T47D human breast cancer cells with high progesterone-receptor levels despite estrogen and antiestrogen resistance. CELL 28:633-642, 1982.

26. Mockus MB, Lessey BA, Bower MA and **Horwitz KB**. Estrogen insensitive progesterone receptors in a human breast cancer cell line: Characterization of receptors and of a ligand exchange assay. ENDOCRINOLOGY 110:1564-1571, 1982.

27. Lessey BA, Alexander PS and **Horwitz KB**. The subunit structure of human breast cancer progesterone receptors: Characterization by chromatography and photoaffinity labeling. ENDOCRINOLOGY 112:1267-1274, 1983.

28. Mockus MB and **Horwitz KB**. Progesterone receptors in human breast cancer: Stoichiometric translocation and nuclear receptor processing. J BIOL CHEM 258:4778-4783, 1983.

29. **Horwitz KB**, Mockus MB, Pike AW, Fennessey PV and Sheridan RL. Progesterone receptor replenishment in T47D human breast cancer cells: Roles of protein synthesis and hormone metabolism. J BIOL CHEM 258:7603-7610, 1983.

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49. **Horwitz KB**. Estrogen receptor mutants and cellular heterogeneity in hormone resistant breast cancer. IX INTERNATIONAL CONGRESS ON ENDOCRINOLOGY: SATELLITE SYMPOSIUM: ZINC FINGER PROTEINS IN ONCOGENESIS, DNA-BINDING AND GENE REGULATION. AMSTERDAM, SEPTEMBER, 1992.

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51. **Horwitz KB**. How do breast cancers become hormone resistant? The Rhone-Poulenc Rorer Clinical Lecture, THE ENDOCRINE SOCIETY, Las Vegas, June, 1993.

52. Jackson TA, Tung L, Takimoto GS and **Horwitz KB**. Antagonist-occupied human progesterone B-receptors activate transcription without binding to a progesterone response element. THE ENDOCRINE SOCIETY, Las Vegas, June, 1993.

53. **Horwitz KB**. How do breast cancers become hormone resistant? ISGSH XVI MEETING, Vienna, Austria, November, 1993.

54. **Horwitz KB**. Agonist effects of antagonist-occupied progesterone B-receptors: New model systems. KEYSTONE SYMPOSIA, Taos, NM, February, 1994.

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58. **Horwitz KB**. Antiestrogens, antiprogestins and hormone resistant breast cancer. KEYSTONE SYMPOSIA, Lake Tahoe, CA, March, 1994.

59. **Horwitz KB**. Agonist effects of antagonist-occupied progesterone B-receptors. 21st GERMAN CANCER SOCIETY CONGRESS, Hamburg, Germany, March, 1994.

60. **Horwitz KB**. Symposium Lecture: Abnormal responses to hormones in breast cancer. AMERICAN ASSOCIATION FOR CANCER RESEARCH, San Francisco, CA, April, 1994.

61. **Horwitz KB**. President's Lecture: Reproductive Hormones and Breast Cancer. THE SOCIETY FOR GYNECOLOGIC INVESTIGATION, Chicago, IL, April, 1994.

62. Tung L, Takimoto GS, Sartorius CA, Groshong SD and **Horwitz KB**. Agonist effects of antagonists on progesterone B-receptors: New models of hormone-resistant breast cancer. THE ENDOCRINE SOCIETY, Anaheim, CA, June, 1994.

63. **Horwitz KB**. Ovarian hormones, antagonists and breast cancer. NORTH AMERICAN MENOPAUSE SOCIETY, San Francisco, CA, September, 1995.

64. **Horwitz KB**. Plenary lecture: Unusual actions of antiprogestins. ERNST SCHERING RESEARCH FOUNDATION, Berlin, Germany, November, 1995.

65. **Horwitz KB**, Bain DL, Groshong SD, Hovland AR, Jackson TA, Lange-Carter C, Richer JK, Sartorius CA, Takimoto GS, Tung L and Wierman A. Progesterone receptor isoforms and variants in breast cancer. NUCLEAR RECEPTORS KEYSTONE SYMPOSIUM, Lake Tahoe, California, 1996.

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67. Richer JK, Wierman AM, Lange-Carter C and **Horwitz KB**. Variant progesterone receptors in human breast cancer cell lines and tumors. NUCLEAR RECEPTORS KEYSTONE SYMPOSIUM, Lake Tahoe, California, 1996.

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75. **Horwitz KB**. Hormones, hormone resistance and breast cancer. Plenary Lecture, AUSTRALIAN SOCIETY FOR MEDICAL RESEARCH, Adelaide, November, 1997.

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85. **Horwitz KB**, Owen GI, Richer JK, Lange C, Tung L and Takimoto G. Breast cancer growth regulation by progesterone and cross-talk with epidermal growth factor. Symposium Lecture, Nuclear Receptor Gene Family, KEYSTONE SYMPOSIA, Lake Tahoe, CA, March, 1998.

86. Graham JD, Tung L, Osborne CK, Fuqua SAW and **Horwitz KB.** Quantitative analysis of nuclear receptor coregulators and hormone resistant breast cancer. 80th Annual Meeting, THE ENDOCRINE SOCIETY, June 24-27, 1998. Abst # OR40-1.

85. Richer JK, Lange CA, Manning NG, Powell RL and **Horwitz KB.** Convergence of progesterone annd epidermal growth factor signaling: Receptors interact with STAT5 and induce their nuclear translocation. 80th Annual Meeting, THE ENDOCRINE SOCIETY, June 24-27, 1998, Abst # OR48-4.

86. Lange CA, Miller KM, Richer JK and **Horwitz KB.** Cross-talk between progesterone and Type I growth factor receptors regulates breast cancer growth. 80th Annual Meeting, THE ENDOCRINE SOCIETY, June 24-27, 1998, Abst # OR49-2.

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90. Richer JK, Graham JD and **Horwitz KB.** The A- and B-isoforms of progesterone receptors determine how progesterone can regulate boh proliferative and differentiative programs. THE ENDOCRINE SOCIETY, June 12, 1999.

91. Graham JD, Tung L, Fuqua SAW, Osborne CK and **Horwitz KB.** Do transcriptional corepressors control tamoxifen resistance in breast cancer? THE ENDOCRINE SOCIETY, June 12, 1999.

92. Bain DL, Franden MA, Takimoto GS and **Horwitz KB.** Structural analysis of the two human progesteerone receptor N-termini explain their isoform-specific functional differences. THE ENDOCRINE SOCIETY, June 12, 1999.

93. Lange CA, Shen T and **Horwitz KB.** Progesterone receptor ubiquitination and ligand-dependent downregulation is due to MAPK phosphorylation of serine 294. THE ENDOCRINE SOCIETY, June 12, 1999.

BIOGRAPHICAL SKETCH

Give the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Carol A. Lange, Ph.D.	Senior Instructor

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Denver University, Denver, CO	B.S.	1985	Biology, Chemistry
University of Colorado, Boulder	Ph.D.	1991	Pharmaceutical Sciences, Molecular Toxicology

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Professional Experience:

1983-87	Medical Technician II, Department of Pathology, Cytogenetics Laboratory, The Denver Children's Hospital
1984-85	Teaching Assistantship, Department of Biology, University of Denver
1988-90	Teaching Assistantships in Molecular and Cellular Pathology and Graduate Core Course, School of Pharmacy, University of Colorado, Boulder
5/91 - 8/95	Postdoctoral Fellow for G.L. Johnson, Ph.D., Division of Basic Sciences, National Jewish Center, Denver, CO
9/95 - 7/96	Instructor/Fellow, Division of Endocrinology, Metabolism and Diabetes, University of Colorado Health Sciences Center, Denver
7/96-1998	Instructor, Division of Endocrinology, Metabolism and Diabetes, University of Colorado Health Sciences Center, Denver
1998-present	Senior Instructor, Division of Endocrinology, Metabolism and Diabetes, University of Colorado Health Sciences Center, Denver

Honors and Awards:

Phi Beta Kappa Honors Society
Graduated Magna Cum Laude (Denver University, 1985)
Rho Chi Pharmacy Honors Society
University of Colorado Research Award in Neuroscience, 1991
Society of Toxicology Platform Presentation Award, 1991
Mechanisms in Toxicology 1992 National Student Competition; Honorable Mention

Selected Scholarships and Fellowships:

1981-1985	Denver University Honors Scholarship
1987-1989	Colorado Doctoral Fellowship
1991-1992	Fulbright Scholarship for Study in Norway
1991-1992	Norwegian Marshall Fund Research Fellowship
1993-1995	Individual National Research Service Award/Postdoctoral Fellowship
1994-1995	American Cancer Society/CU Cancer Center Seed Grant Award
1996-1997	Colorado Cancer League Young Investigator Fellowship

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Lange-Carter CA, Fossli T, Jahnsen T and Malkinson AM. Decreased expression of the type I isozyme of cAMP-dependent protein kinase in tumor cell lines of lung epithelial origin. J Biol Chem 265:7814-7818, 1990.

Lange-Carter CA and Malkinson AM. Alterations in the cAMP signal transduction pathway in mouse lung tumorigenesis. Exp Lung Res 17:325-341, 1991.

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Lange-Carter CA, Pleiman CM, Gardner AM, Blumer KJ and Johnson GL. A divergence in the MAP kinase regulatory network defined by MEK kinase and Raf. Science 260:315-319, 1993.

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Gardner AM, Vaillancourt RR, **Lange-Carter CA** and Johnson GL. MEK-1 phosphorylation by MEK kinase, Raf and MAP kinase: Analysis of phosphopeptides and regulation of activity. Molec Biol Cell 5:193-201, 1994.

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Minden A, Lin A, McMahon M, **Lange-Carter CA**, Derijard B, Davis RJ, Johnson GL and Karin M. Bifurcation in Ras signalling: Raf-1 and MEKK-1 differentially activate ERK and JNK MAP kinases. Science 266:1719-1722, 1994.

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Russell M, **Lange-Carter CA** and Johnson GL. Recognition of recombinant MEK-1 and MEK2b expressed in E. Coli. Biochemistry 34:6611-6615, 1995.

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Xu S, Robbins D, Frost J, Dang A, **Lange-Carter CA** and Cobb M. MEKK1 phosphorylates MEK1 and MEK2 but does not cause activation of mitogen-activated protein kinase. Proc Natl Acad Sci USA 92:6808-6812, 1995.

Johnson NL, Gardner AM, Diener KM, **Lange-Carter CA**, Gleavy J, Jarpe MB, Minden A, Karin M, Zon LI and Johnson GL. Signal transduction pathways regulated by mitogen-activated/extracellular response kinase kinase kinase induce cell death. J Biol Chem 271:3229-3237, 1996.

Richer JK, **Lange-Carter C**, Wierman AM, Brooks KM, Jackson TA, Tung L, Takimoto GS and Horwitz KB. Novel progesterone receptor variants in breast cancers and normal breast cells repress transcription by wild-type receptors. Breast Cancer Res Treat 48:231-241, 1998.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Jennifer Richer, Ph.D.	Senior Instructor

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
University of Texas, El Paso	BS	1986	Biology, Chemistry
University of Texas, El Paso	MS	1988	Biological Sciences
Colorado State University, Fort Collins	Ph.D.	1992	Pathology

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

Professional Experience:

1998-present Senior Instructor, University of Colorado Health Sciences Center, Denver
1995-1998 Instructor Fellow, University of Colorado Health Sciences Center, Denver
1994-95 Postdoctoral Fellow, University of Colorado Health Sciences Center, Denver
1992-94 Postdoctoral Fellow, New England Biolabs, Beverly, MA
1988-92 Research Assistant, Department of Pathology, Colorado State University, Ft. Collins, CO
1987-88 Teaching Assistant, Department of Biological Sciences, University of Texas at El Paso, TX

Honors and Awards:

1995-96 Thorkildesen Research Fellowship, University of Colorado Health Sciences Center, Denver, CO
1992-94 Co-Investigator, SBIR Grant, New England BioLabs
1988-91 USDA Biotechnology Training Grant- Colorado State University
1991 Travel Grant, American Society of Parasitologists 66 Annual Meeting
1991 Best Student Presentation-Rocky Mountain Conference of Parasitologists
1990 Colorado Graduate Fellowship, Cell & Molecular Biology Interdisciplinary Program, Colorado State University
1987-88 University Graduate Scholarship, University of Texas
1987-88 President, Tri-Beta Biological Honor Society, Delta Phi Chapter
1982-86 Member, University of Texas at El Paso Honors Program
1982-84 Undergraduate Scholarship, University of Texas at El Paso

Membership in Professional Societies and Service*

Endocrine Society
American Association for Cancer Research
*Komen Foundation, Denver Chapter, Newsletter contribution and Pink Tie Affair Committee

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Richer, J., Mayberry, L.F., and J.T. Ellzey. 1991. Comparative ultrastructural alterations induced in rat intestinal mucosa by *Eimeria separata* and *E. nieschulzi* (Apicomplexa: Eimeriidae). Transactions of the American Microscopical Society **110**: 262-268.

Richer, J.K., Sakanari, J.A., Frank, G.R. and R.B. Grieve. 1992. Proteases produced by third- and fourth-stage larvae of *Dirofilaria immitis*. Exp. Parasitology **75**: 213-222.

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Jackson, T.A., **Richer, J.K.,** Bain, D.L., Takimoto, G.S., Tung, L. and Horwitz, K.B. 1997. The partial agonist activity of antagonist-occupied steroid receptors is controlled by a novel hinge-domain binding coactivator, L7/SPA and the corepressors N-CoR or SMRT. Molec Endocrinol 11:693-705.

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Leslie, K.K., Kumar, N.S., **Richer, J.K.**, Owen, G.I., Takimoto, G.S., Horwitz, K.B., and Lange, C. 1997. Differential expression of the A and B isoforms of progesterone receptors in human endometrial cancer cells. Ann NY Acad Sci 827:17-26.

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Owen, G.I., **Richer, J.K.**, Tung, L., Takimoto, G.S., and Horwitz K.B. 1998. Progesterone regulates transcription of the $p21^{WAF1}$ cyclin-dependent kinase inhibitor gene through Sp1 and CBP/p300. J Biol Chem 273:10696-10701

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Lange, C.A., **Richer, J.K.**, Shen, T., and Horwitz, K.B. 1998. Convergence of progesterone and epidermal growth factor signaling in breast cancer. Potentiation of mitogen-activated protein kinase pathways. J Biol Chem 273:31308-31316.

Richer, J.K., Lange, C.A., Manning, N.G., Owen, G.I., Powell, R.L., and Horwitz, K.B. 1998. Convergence of progesterone with growth factor and cytokine signaling in breast cancer. Progesterone receptors regulate Stat5 expression and activity. J Biol Chem 273: 31308-31316.

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Lange, C.A., **Richer, J.K.**, and Horwitz K.B. 1999. Hypothesis: Progesterone primes breast cancer cells for cross-talk with proliferative or antiproliferative signals. Molec Endocrinol In Press.

Presentations

Richer, J., Hough, D.M. and Maina, C.V. 1994. Ecdysone receptor and other NHR's in nematodes. Keystone Symposia on Molecular and Cellular Biology: Steroid/Thyroid/Retinoic Acid Super Gene Family. (Abstract No. 427, J Cellular Biochemistry).

Richer, J., Lange-Carter, C., Wierman, A.M. and Horwitz, K.B. 1996. Variant progesterone receptors in human breast cancer cell lines and tumors. Steroid/Thyroid/Retinoic Acid Gene Family, Keystone Symposia, Lake Tahoe, CA. (Abstract No. 150).

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