Pathobiological Considerations Relating to the Treatment of Intraductal Carcinoma (Ductal Carcinoma in Situ) of the Breast

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Introduction

Recent publications about intraductal carcinoma of the breast (ductal carcinoma in situ, DCIS) convey the misperception that it may be as ominous as invasive cancer. The natural history of DCIS is generally regarded as perplexing because of this lesion’s heterogeneity. Indeed, DCIS might more aptly signify dilemma, consternation, inconsistency, and superficiality.

Lumpectomy

One of the principal dilemmas concerning DCIS relates to its treatment. The debate in this regard is reminiscent of that enacted more than a decade ago when lumpectomy was proffered as an alternative to mastectomy for the primary surgical treatment of invasive breast cancer. In the latter, as well as in DCIS, two contraindications have been cited: multicentricity, defined as cancer in quadrants remote from the index lesion (unlike multifocality, in which cancer occurs within the same quadrant as the index lesion), and ipsilateral breast tumor recurrence (IBTR).

Most consternation about multicentricity has been derived from pathologic studies of breasts removed for biopsy-proven DCIS, which reveal a relatively high incidence of this phenomenon. Its frequency accompanying DCIS appears no greater than that observed in comparable studies of breasts harboring invasive cancer. Yet, a marked inconsistency exists between its occurrence in breast specimens and its biologic or clinical expression.

Almost all cases of IBTR observed after lumpectomy (with or without subsequent local breast irradiation) for invasive cancer or DCIS occur at or near the site of the index cancer rather than in remote quadrants. Indeed, IBTR after local removal of DCIS as with invasive cancer appears to truly represent “residual” cancer or that developing at the site of a prior attempt at surgical removal. It is viewed as a geographic oversight resulting from the multifocal growth pattern of many breast cancers. In support of such a contention is the recognition that when DCIS is present in the IBTR, it is similar to that of the index cancer.

One of the caveats concerning lumpectomy for the treatment of DCIS relates to the natural history of the component of invasive cancer found in approximately 25 percent of IBTR after lumpectomy and irradiation and in 33 percent after lumpectomy alone. Although it is conventionally attractive to consider that these invasive cancers developed from the DCIS, there is no unequivocal evidence to support such a contention. In many instances, the temporal relationship between the removal of the index DCIS and the development of an
IBTR with invasive cancer appears unduly brief. It is equally if not more plausible that invasive cancer at least in part results from overlooked invasive foci with or without DCIS, as noted earlier. As long ago as 1960, Gillis and associates demonstrated such invasive foci in mastectomy specimens from patients with DCIS only after exhaustive examination. These authors reemphasized Muir’s much earlier caution concerning such occult invasive foci in some lesions otherwise regarded as pure DCIS. Subsequently, similar pathologic studies have reaffirmed these observations.

The often-cited studies of Betsill and Page and their associates relating to this issue appear somewhat unusual. They uncovered 25 and 28 examples of DCIS, respectively, in their pathologic review of breast biopsies previously considered to demonstrate only benign disease. Ten of the 15 patients followed by the former exhibited IBTR. Four of the 10 (40 percent) died of breast cancer or were alive with evidence of the disease. Seven of 25 patients (27 percent) followed by Page and associates developed IBTR. Four of the seven (57 percent) succumbed to breast cancer.

I know of no other study that has revealed such high incidences of mortality related to DCIS with or without IBTR. Yet, these highly retrospective analyses unfortunately have been regarded as evidence indicating the need for mastectomy for DCIS.

From a practical therapeutic standpoint, it cannot be sufficiently emphasized that despite IBTR with an invasive component after lumpectomy, survival of patients with DCIS has been repeatedly estimated to be 95 percent or greater. Further, the two deaths related to breast cancer observed thus far in our study occurred in women without IBTR. The survival estimate is equal to or even greater than that cited for patients with DCIS treated by mastectomy. It is worthwhile recalling that survival after lumpectomy with or without irradiation is also similar to that noted after mastectomy for invasive cancer despite a 35 percent incidence of IBTR in the lumpectomy-only group and a 10 percent incidence in the lumpectomy-irradiation group after 12 years of observation.

**Prediction of Ipsilateral Breast Tumor Recurrence**

The misunderstanding concerning the biological and clinical significance of IBTR has led to an inordinate preoccupation of students of the disease with attempts to identify pathologic or other features that might be considered predictive of such an event. One assumes that if these attempts were successful, IBTR could be forestalled by mastectomy, although as noted previously, IBTR per se is not attended by any pejorative biologic effect.

**Comedo Ductal Carcinoma in Situ**

One of the frequently cited studies in this regard was recorded in 1989, at least five years after lumpectomy became well established as a primary surgical treatment of invasive cancer. It was concluded on the basis of 37 breasts removed for impalpable DCIS and 13 with DCIS and microinvasion that the comedo type of DCIS was more frequently associated with microinvasion and multicentricity. Two suggestions by the authors were overlooked, however. The first was that comedo DCIS was best treated by mastectomy and axillary dissection. The second was based on the observation that the papillary and micropapillary forms of DCIS were also more frequently noted with multicentricity but not microinvasion; this prompted the suggestion that these forms of DCIS could be treated by mastectomy without axillary dissection. Women with nonpalpable cribriform or solid types might be treated by excision only if the biopsy disclosed involvement.
of only a “small number” of ducts. What constituted a “small number” was not stated. The very small sample sizes, the retrospective nature of the study, the failure to recognize the inconsistency between pathologic frequency and clinical or biologic events, the vagary of criteria such as that for microinvasion, and the lack of statistical confirmation of differences characterize such information as being too superficial to warrant any therapeutic conclusions. It also fails to provide evidence that the comedo type of DCIS is more aggressive or ominous than other forms.

Another study based upon examination of breast specimens provides results similar to those mentioned earlier but also included larger (more than 2.5 cm) examples of DCIS, some of which were palpable. Therapeutic advice based upon only 20 instances in which the DCIS was treated by lumpectomy is quite bizarre in the context of today’s understanding of DCIS and lumpectomy. It is important to recognize that the DCIS uncovered by Betsill and Page and associates in their somewhat aberrant studies was non-comedo and their sizes, although not stated, were presumably microscopic. It is also of historical interest that Bloodgood, who was one of the first to utilize the designation comedocarcinoma, indicated the relative banality of “pure” comedocarcinoma (called comedo-adenoma) as opposed to instances in which it was associated with invasive cancer and alluded to its control by excision only. Solin and associates initially observed comedo DCIS to be predictive for IBTR at seven years but not at 10 plus years.

We have advocated for at least a decade elimination of the designation comedo DCIS because it is not a singular entity. In truth, comedo necrosis per se may be found in almost all subtypes of DCIS classified according to topographical or architectural features or may be associated with DCIS whose cells exhibit good or poor nuclear grade. Further, it may vary from being absent or slight (involving less than one third of ducts involved with DCIS) or moderate to marked with more extensive involvement. All of these factors punctuate the inadequacies of classification of DCIS depending on the presence or absence of comedo DCIS.

**Classification Systems**

Another proposal divided DCIS into high grade/large cell or low grade/small cell. Although such grouping of DCIS has been regarded to reflect its heterogeneity, it appears to me to do the con-
trary, namely, oversimplify its complexity or heterogeneity. The consideration of grade with cell size is redundant because grade is commensurate with cell size, although the latter is more accurately manifested by its nucleus and thus its nuclear grade. No evidence exists to indicate that such combinations provide any more significant information about the natural history of DCIS than consideration of its individual characteristics. Studies purporting to demonstrate a relationship between IBTR and nuclear grade are also somewhat dubious when it is appreciated that the authors utilized a method of assessing histologic rather than nuclear grade per se. More recently a classification has been proposed based upon architectural differentiation via a vis degree of polarization of neoplastic epithelial cells and cytonuclear differentiation. It has been regarded as more consistent or reproducible than the conventional architectural subtyping or presence or absence of comedo necrosis. Despite claims to the contrary, it manifests its subjectivity as do most classifications or grading systems utilizing three groups, one of which is “intermediate.” It has not been clinically tested and appears to be somewhat ponderous and strained.

Invasive Carcinoma Associated with Ductal Carcinoma in Situ

The difficulty of pathologically distinguishing between intraductal hyperplasia and DCIS has long been recognized. My consultative practice and NSABP experience have revealed an equally if not greater dilemma concerning the identity of so-called microinvasion arising from...
DCIS. Indeed, in practice it represents one of if not the most commonly over-diagnosed events in the pathology of breast cancer. Its validity as an entity, unfortunately, has been considered strengthened by reference to the ultrastructural study of DCIS by Ozzello that describes defects in the ultrastructural basement membrane of affected ducts. However, his as well as my electron microscopic investigations do not reveal extension of neoplastic cells through such altered foci.

As I have previously pointed out, it is an extremely uncommon event to appreciate such stromal extension in histologic sections. It is infinitely easier to relate what microinvasion is not than what it is. The presence of carcinoma either extending into or arising de novo from lobular ductules (lobular cancerization) may simulate, and has frequently been mistaken for, an invasive component (Fig. 1). DCIS may exhibit budding into the stroma. This form of pseudoinvasion results from a plane of section because basement membrane can be demonstrated by appropriate stains to be continuous about the bud and the major portion of the involved duct (Fig. 2). Regressive changes in DCIS characterized by periductal sclerosis and lymphocytic infiltrate may be accompanied by destruction of the wall. Clusters and individual neoplastic cells may appear to be floating freely in “comedo” debris (Fig. 3A). Sometimes such cells may be surrounded by breast stroma (Fig. 3B). Both impart an erroneous impression of invasion. Solitary, or even loosely cohesive, groups of cells may be found in the stroma of DCIS (Fig. 4). Such elements are often regarded as evidence of microinvasion. Although worrisome in this regard, they most often fail to unequivocally satisfy criteria for malignant tumor cells.

A striking illustration of this is found in the often-cited report of Wong and associates, who studied 41 patients with DCIS and purported microinvasion. None had nodal metastases, IBTR, or deaths related to breast cancer. This is not surprising because their photomicrograph depicting microinvasion appears to represent a portion of a duct with what seems to me to represent, at most, atypical ductal hyperplasia. The microinvasion that is highlighted represents two or three blurred, unidentifiable cells within its adjacent stroma. DCIS with microinvasion has been vaguely described as a predominantly intraductal cancer showing “either focal invasion below the basement membrane in one or several ducts or up to 10% of the surface of the histological sections showing more advanced stromal invasion.” The Royal College of Pathologists also indicates DCIS with microinvasion to be “predominantly non-invasive with one or more foci of invasive carcinoma, none measuring more than 1.0 mm.” One wonders what type of invasive cancer it would be if it added up to 5.0 or 10.0 mm. Lastly, microinvasion has been regarded as “early” invasion with a maximal extent of 2.0 mm or invasive cancer less than 10 percent of the tumor.

First, there is no way to discern whether such invasion is or is not biologi-
cally early. Second, 10 percent of a large DCIS could represent an invasive cancer of at least 5.0 mm. Indeed, such a small size may actually represent only slightly less than 75 percent of the tumor’s natural history and would be biologically late.

Our criterion for invasive cancer associated with DCIS is an attempt to circumvent these inadequacies by requiring a well-recognized histologic type of invasive cancer to be present (Fig. 5). If it is less than 1.0 cm, it is regarded as “small,” but its actual measurement is indicated. We regard the invasive component accompanying DCIS to represent the principal diagnosis of such a combination. Forty percent of overt invasive carcinomas of the breast may contain a moderate to marked component of DCIS.

The natural history of such small invasive cancers associated or unassociated with DCIS has not been satisfactorily elaborated. Silverberg and Chitale noted that prognosis was better for invasive carcinoma estimated to consist of less than 10 percent of the predominately DCIS tumor (apparently the source of the 10 percent cited by Wong and associates in their definition of microinvasion) than for invasive carcinoma in which the DCIS represented smaller proportions. Yet, such small invasive cancers were found to be accompanied by a modest incidence of nodal metastasis and mortality, whereas no adverse events were noted in the patients with “pure” DCIS. Our study failed to reveal any survival advantage for invasive cancers with a moderate to marked DCIS component when compared with those that had less DCIS content. Yet, our estimate was not comparable to that of Silverberg and Chitale since the moderate to marked estimation represented 65 to 99 percent DCIS. Seidman and associates failed to find any nodal metastasis from DCIS that also contained invasive cancers measuring 0.5 cm or less (0/11), whereas two of nine were found when the invasive component measured 0.5 to 1.0 cm. It is obvious that further information is needed about non-palpable (1.0 cm or less) invasive cancers with or without associated DCIS before definitive therapeutic decisions are proposed for such lesions.

Localized Ductal Carcinoma in Situ with Remote Calcifications

The management of patients with localized DCIS and remote calcifications represents another therapeutic dilemma. It has been suggested that such a situation might best be treated by mastectomy and axillary dissection. This represents, in my opinion, another overreaction to the
purported potential of multicentricity. The distinct possibility that such diffuse lesions if indeed neoplastic may be treated by tamoxifen or local breast irradiation, or both, should be resolved by the results of NSABP protocol B-24, which addresses this issue. The inconsistency between pathologic and clinical importance of multicentricity in DCIS is worthy of reemphasis, as is recognition that lumpectomy is a cosmetic procedure. Its only contraindication is a disproportionate relationship between the size of the tumor and the breast, which might produce poor cosmesis.

Margins of Resection

Another source of pathologic and therapeutic consternation relating to DCIS (and to invasive breast cancer treated by lumpectomy) is the assessment of margins of resection. It is generally held that the resected tumor margins removed by lumpectomy should be free of tumor cells. Yet, there is no compelling evidence to indicate how wide or free would be optimal. Indeed, most reports in this regard are not only vague but confusing. In one often-cited study, margins were considered negative when tumor was more than 2 mm from the inked surface or when no tumor was found in the reexcisional tissue, presumably representing a completion lumpectomy. Margins were considered positive when tumor was found “at” the inked margin and close when tumor was not “at” the margin but less than 2 mm from it. Importantly, the authors’ own data do not provide a basis for the use of 2 mm as the criterion. Also, the word “at” could literally represent tumor being on, in, or near the margin. Our assessment of the status of margins in their cohort indicates them to be free in only 67 percent. The high incidence of involvement may well account for the 17 percent incidence of IBTR, which is strikingly high for a cohort treated by lumpectomy and irradiation. Unfortunately, adoption of a free margin of more than 2 mm as appropriate would prompt an inordinate number of completion lumpectomy procedures. Lastly, appraisal of their data reveals that results relating to close margins would be the same regardless of whether they are included with those estimated to be free or involved.

The uncertainty about assessment of margins has prompted us for the past 10 years to regard tumor transection as the only indicator of involvement for both invasive cancer and DCIS (Fig. 6). Thus far, our observed incidence of IBTR does not exceed that recorded by others, which would be expected if such a practice represented an underestimate. This approach excludes the highly subjective pathologic incantations of tumor being “too close,” “very close,” or as noted earlier “at” the margins of resection. It further allows the pathologist to assess the margins when the specimen has not been inked, a practice that unfortunately still occurs. My conviction about “close” is best represented by the simple, well-recognized rule of thumb that “close” only counts in horseshoes.
| Specimen Margins | Comedo Necrosis       | No. at Risk | No. of Events | Average Annual Rate/100 | No. at Risk | No. of Events | Average Annual Rate/100 |
|------------------|-----------------------|-------------|---------------|-------------------------|-------------|---------------|-------------------------|
| Free             | Absent/ Slight        | 125         | 9             | 1.97                    | 144         | 6             | 1.18                    |
| Free             | Absent/ Slight        | 98          | 16            | 5.44                    | 105         | 4             | 1.18                    |
| Uncertain/ involved | Absent/ Slight      | 26          | 5             | 5.95                    | 24          | 2             | 2.10                    |
| Uncertain/ involved | Moderate/ Marked    | 25          | 8             | 10.46                   | 26          | 3             | 3.28                    |

Adapted with permission from Fisher et al.9

| Type               | Localized | MX | L | XRT | AXD | Adjuvant |
|--------------------|-----------|----|---|-----|-----|----------|
| Pure DCIS*         | +         | –  | + | +   | –   | –        |
| + and remote CALC  | –         | +  | + | –   | –   | ? TAM    |
| DCIS + Invasive    | ≤0.5 cm†  | +  | – | +   | +   | ?        |
|                    | 0.6 to 1.0 cm† | + | – | +   | +   | LN neg, ? |
|                    | >1.0 cm†  | +  | – | +   | +   | LN neg, + |

*Also for so-called ductolobular carcinoma in situ.
†Size of invasive component.

MX = mastectomy, L = lumpectomy, XRT = radiation therapy, AXD = axillary dissection, DCIS = ductal carcinoma in situ, CALC = calcifications, TAM = tamoxifen, LN = lymph node, ? = no firm data
My analyses of tissue removed in completion lumpectomies that were preceded by “biopsy” disclosed tumor in 24 percent when the margins were considered free. Residual tumor was found in 50 percent and 62 percent when the biopsy margins were considered uncertain or involved, respectively. Thus, completion lumpectomy was hypothetically unnecessary in 76 percent of instances of the two-stage procedure. Residual tumor in completion lumpectomies was not related to IBTR. Biopsies that are not excisional vis a vis lumpectomies appear to be anachronistic. Assessment of the status of the margins is relatively crude yet important from a prognostic standpoint.

Irradiation After Lumpectomy

Our definitive pathologic studies of DCIS were performed on 573 women enrolled in protocol B-17 of the National Surgical Adjuvant Breast Project (NSABP). This prospective clinical trial has clinically demonstrated that local breast irradiation was effective in reducing IBTR after lumpectomy by at least 33 percent. Nine pathologic factors that might be predictive for IBTR were individually analyzed. Contrary to the view of others, such an approach is statistically and philosophically correct, as reflected in the following remarks made in 1957 by one of the most prominent oncologic pathologists of our time, F.W. Stewart: “The function of cancer research is to break down the complex into analyzable parts, measurable parts, even when one does not necessarily understand something after it has become measured and perhaps can do nothing for a long time after understanding is reached.” This approach really establishes heterogeneity, the present day buzz word relating to DCIS.

The average annual hazard rates for IBTR were lower for all characteristics in patients who were also irradiated than in those treated by lumpectomy only. Uni- variate Cox analyses revealed that the highest rates for IBTR were associated with moderate to marked comedo necrosis, poor nuclear grade, solid histologic type, and uncertain or involved margins. However, multivariate regression revealed only comedo necrosis and margin status to be independent predictors for IBTR. Importantly, I failed to find any significant relationship between tumor size measured either grossly (those not grossly measurable were regarded as being less than 1.0 cm) or microscopically and IBTR. Total agreement between gross and microscopic estimates was poor and occurred in only 59 percent. On the other hand, it was surprisingly high (93 percent) for tumors grossly estimated to be less than 1.0 cm. The annual hazard rate for IBTR was highest for patients whose tumors exhibited both uncertain or involved margins and moderate to marked comedo necrosis when the margins were assessed as free. This preponderant effect of free margins on outcome indicates the need to evaluate their status unless proven to the contrary. In addition, this information also magnifies the significance of irradiation in reducing IBTR. Indeed, we have found no factor or factors as yet that indicate this modality may not be necessary.

VAN NUYS PROGNOSTIC INDEX

On the other hand, there does appear to be an effort to identify instances of DCIS that may not require irradiation. Such an indicator, called the Van Nuys prognostic index (VNPI), has recently been projected as resolving this dilemma. It is based on three gradations of tumor size ($1 = “small” tumors of 15 mm or less; $2 = 16$ to $40$ mm; $3 = 41$ mm or more); degree of tumor free margins ($1 = 10$ mm or more; $2 = 1$ to $9$ mm; $3 = less than 1$
mm); and pathologic classification (3 = nuclear grade 3; 2 = nuclear grade 1 or 2 with comedo necrosis; 1 = nuclear grade 1 or 2 without comedo necrosis). Among patients with total scores for the three variables of 3 or 4, only 2 of 101 (two percent) developed IBTR. However, IBTR occurred in of 40 of 209 patients (19 percent) with a sum of 5, 6, or 7, and 13 of 23 (57 percent) with a score of 8 or 9. Average follow-up was eight years. There was no significant difference in the probability of IBTR for those who did or did not receive local breast irradiation when the VNPI was 3 or 4. Thus, it was concluded that such patients did not require irradiation after lumpectomy.

On the other hand, IBTR for the intermediate group was significantly higher for patients who did not receive irradiation. Despite small numbers, IBTR was also reduced by irradiation in the group with the highest VNPI, but the actual incidence was regarded as high. Accordingly, mastectomy was advised for this group. It was concluded that such subset analysis not only revealed patients with DCIS who do not require local breast irradiation but also better accounted for the heterogeneity of DCIS than analyses based on single factors.

The retrospective subsetting of an extremely retrospective data base as well as other deficiencies in this provocative study prompt me to regard its results with caution. No real analytical reason for selecting the different variables was presented except that they appeared to be observed in previous retrospective analyses, which I have indicated here and elsewhere to be in themselves flawed. One might inquire if the factors selected were independent or interrelated discriminants. The authors state that two of the variables selected, nuclear grade and comedo necrosis, correlate with other biologic markers found in DCIS. It is true that ERBB2, estrogen and progesterone receptors, and DNA content DNA content in DCIS may be variable or may reflect “heterogeneity.” However, their relationship to outcome was not demonstrated for their cohort, and it has not been demonstrated by others for DCIS. Their prognostic role for invasive cancer has not been consistently demonstrated.

Parenthetically, one might cogently inquire why such studies are almost invariably performed for DCIS unless they represent some delusion of precision or unrealistic sophistication. The VNPI authors combined patients from two distinct centers in their data base. Surprisingly, this was considered to strengthen their results. Their failure to provide the reader with an account of patient and tumor characteristics at the two institutions is an important oversight. It is well known that the procedures used in one institution may not be common in another. This suspicion only magnifies the bias of the study, which incidentally was admitted by the authors.

Interestingly, the size of many tumors was quite large. I do not believe many would regard tumors measuring 1.5 cm to be small as suggested. More impor-
tantly, excision of a tumor measuring 4 cm with a margin of 1 cm or more on two aspects would most likely require a quadrantectomy, a poor cosmetic procedure, rather than lumpectomy.

A more detailed account of the various surgical procedures as well as adjuvant therapy that may have been used is essential to deflect criticisms of bias. I also agree with Schnitt et al,43 who formally reviewed this presentation, that it would be essential to know whether the scores for each factor evaluated are equivalent. It would also be important to learn whether the follow-up for each index group was comparable.

Our calculations suggest that mastectomy would be performed unnecessarily in more than half of the patients with VNPI 8 or 9, a group that incidentally possesses too few patients upon which to base a therapeutic decision. Of course, one suspects that the tumors with the high VNPI were inordinately large and would require mastectomy for the simple reason that good cosmesis would not be otherwise obtained.

Lastly, the authors imply that identifying patients with DCIS who do not need local breast irradiation eliminates its untoward side effects (such as changing the texture of the breast) and precludes subsequent irradiation. In our experience, however, alteration of breast texture is most unusual if irradiation is performed correctly. Indeed, such a statement provokes inquiry as to the details of the administration of irradiation, which were not provided. Although irradiation has been utilized after lumpectomy for more than a decade, I am unaware of any systematic reports concerning significant untoward effects of this modality that would contraindicate its use. More controlled studies appear to be essential before such a scheme is adopted for the treatment of DCIS.

Treatment Modalities

The modalities for treatment of DCIS, based upon the most scrutinizable evidence discussed in this presentation, are summarized in Table 2. Unproved procedures for certain situations are duly indicated. In this category is the in situ lesion that we call ductolobular carcinoma in situ (DLCIS), which may represent a “third form” of in situ breast cancer (Fig. 7).44 In our experience, as well as that of others,45-47 such lesions may provoke nosologic difficulty because they possess monomorphic cells found in lobular carcinoma in situ (LCIS) not only in ductules but in larger ducts of the same ductolobular unit. Importantly, the LCIS-type cells exhibit a cribiform pattern, comedo necrosis or sebaceous-like cells reminiscent of DCIS in the large ducts. Some examples of so-called endocrine DCIS described and depicted by Tsang and Chan48 appear to represent DLCIS. Because of its putative ductal element we have suggested postoperative local breast irradiation, as for the more classic forms of DCIS, to be appropriate for its treatment until demonstrated to the contrary.

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American Cancer Society Grants for Targeted Research Request for Applications

The American Cancer Society is pleased to announce its request for applications for its 1997 grants for targeted research.

Grants for research in behavioral, psychosocial, and quality of life relating to prostate cancer and grants for health policy and outcomes research in prostate cancer are open to independent investigators at any stage of their career. Grants will be for three years with up to $250,000 per year, including 25 percent indirect costs, and will be renewable as long as the research remains a targeted priority area. For more information on these grants, call Dr. Ralph Vogler (404-329-7542) or Dr. Frank Baker (404-329-7795).

Grants for research on novel ideas in prostate cancer cell biology are open to investigators at any stage of their careers. Grants will be for three years with up to $65,000 per year, including 25 percent indirect costs, and will not be renewable. For more information, contact Dr. Peter Ove (404-329-7552).

Contact the office of sponsored programs at your institution for a special RFA application form or download one from http://www.cancer.org. The first deadline is April 1, 1997, with a subsequent deadline on October 15, 1997, and on those same dates through 1999.