

Pure Small Cell Carcinoma of the Urinary Bladder

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A 58-year-old Hispanic man presented with a 1-week history of right-leg swelling, lower abdominal discomfort, and one episode of painless gross hematuria. Physical examination revealed a bulge on the right side of the lower abdomen. On percussion, dullness was appreciated on the supra pubic and the right side of the umbilical area, and a large mass was palpated on the lower abdomen. Laboratory data revealed hemoglobin of 6.3 g/dL and red blood cells (RBCs) in the urine analysis. Urine cytology revealed malignant cells. Computed tomography (CT) of the abdomen and pelvis revealed a large solid pelvic mass (21 × 14 × 17 cm) with invasion of the posterior bladder wall, left para-aortic and right external iliac lymphadenopathy, and left hydronephrosis (Figure 1). There was no evidence of distant metastasis. A percutaneous left nephrostomy tube was placed. Cystoscopy revealed a large bladder lesion, and a core biopsy of the mass was done. Pathologic examination revealed small cell carcinoma (SCC). Immunohistochemical staining was positive for chromogranin A (CHR), synaptophysin (SYN), and neural and neuroendocrine markers (CD56) and negative for thyroid transcription factor-1 and leukocyte common antigen (Figures 2 and 3). The patient was treated with 10 cycles of systemic chemotherapy with a combination of carboplatin and etoposide, followed by a course of radiation directed to the pelvic mass. The patient tolerated the treatment well, and imaging surveillance for 18 months after completion of the treatment showed significant interval reduction in the size of the tumor to 7 cm and no evidence of recurrence (Figure 4). However, the patient returned with seizures at 18 months and was found to have brain metastasis. Whole-brain radiation in addition to steroids was initiated; however, the patient developed septicemia



Figure 1. Pelvis, large pelvic mass, invading the posterior wall of the urinary bladder wall, and large diverticulum.

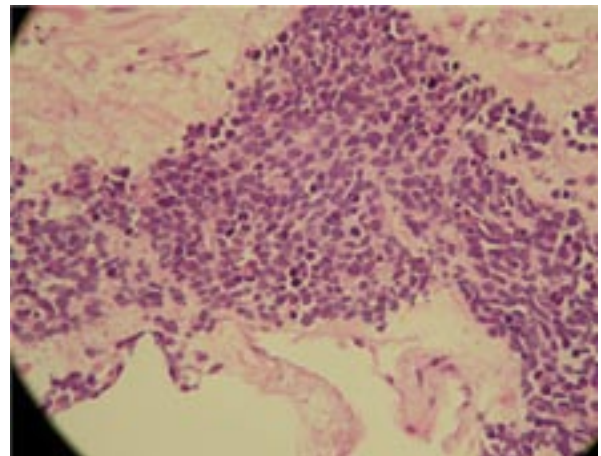


Figure 2. Hematoxylin and eosin staining of the biopsy specimen.

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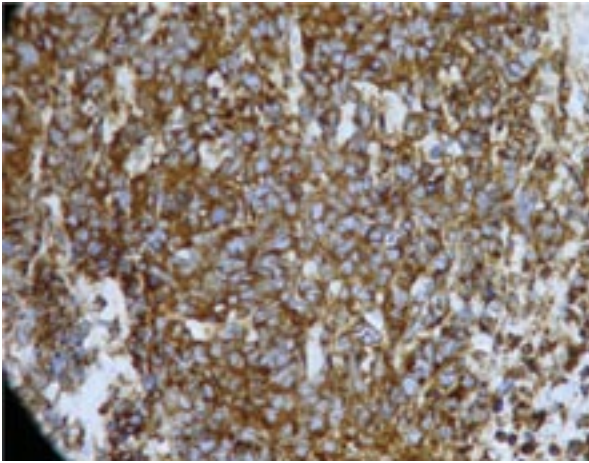


Figure 3. Synaptophysin staining.

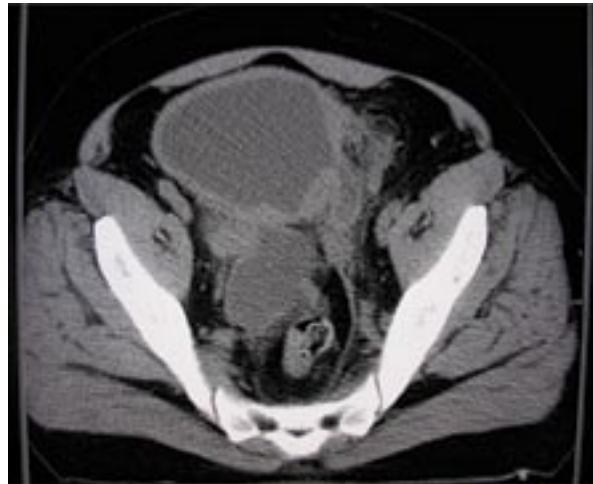


Figure 4. Interval reduction in the tumor size after chemoradiation therapy.



Figure 5. Bilateral common femoral vein thrombosis.

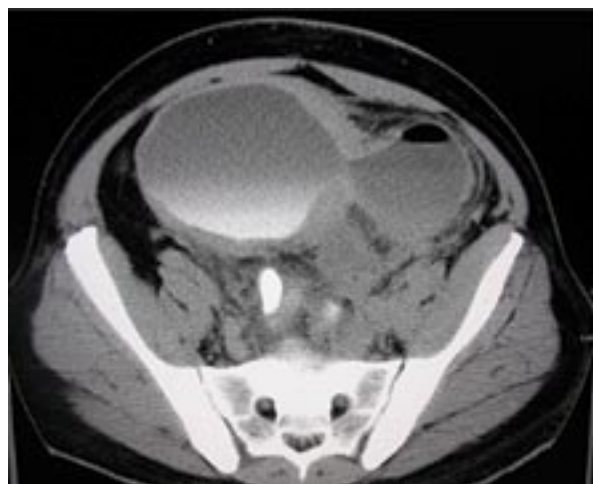


Figure 6. Post-void phase with IV contrast.

during a long and complicated course of hospitalization and eventually expired.

Background

More than 60,000 new cases of bladder carcinoma are expected annually in the United States. Urothelial carcinomas account for the vast majority of these tumors.¹ SCC is also termed undifferentiated carcinoma, small cell anaplastic carcinoma, neuroendocrine SCC, and oat cell carcinoma.^{2,3,4} SCC of the bladder (SCCB)

accounts for 0.35–0.70% of all bladder tumors. The male:female ratio has been reported between 2:1 and 5:1 in different studies.¹⁻²⁰ This highly aggressive tumor usually affects frail, elderly patients with significant comorbidities in their sixth to eighth decade of life, with a median age of 74 years (range, 36–83 years).^{1,5,7,8,21}

In 1926, Barnard described the first case of SCC, originating in the lungs. Today, small cell lung cancer (SCLC) accounts for approximately 90,000 of the 150,000 annual cases of lung cancer in the United States. In 1930, Duguid and Kennedy described nonpulmonary

SCC for the first time.²² The existence of SCCB was first mentioned by Koss in 1975, but it was Cramer and colleagues who reported the first case of primary SCCB in a 69-year-old male with hypophosphatemia in 1981.²³ Since then, 286 cases of SCCB have been diagnosed according to World Health Organization (WHO) criteria and published in the literature.^{2,6,14,22,23}

It seems probable that virtually any epithelial-derived surface or glandular tissue may give rise to SCC.²¹ Extrapulmonary SCC has been well described at sites as diverse as the gastrointestinal tract, pancreas, thymus, paranasal sinuses, oropharyngeal mucosa, pharynx, larynx, trachea, salivary glands, skin, breast, uterus, cervix, prostate, kidneys, and ureters.^{1-3,5,7,8,16,22,24,25} In SCCB, unlike in SCLC, there are a higher proportion of mixed small cell and non-small cell carcinomas. The non-small cell elements are typically urothelial or glandular, with or without carcinoma in situ.⁷ Primary extrapulmonary SCC shares similar microscopic and immunohistochemical features with SCLC^{2,4,22} and behaves aggressively.⁵

Etiology

Although tobacco smoking has been reported as an etiologic factor in 65% of patients, the cause of primary SCCB is unknown.^{1,2,5,9-16} Different hypotheses have been proposed. 1) There is malignant transformation of bladder neuroendocrine cells into SCCB,^{8,19} which may be explained by mixed histologic patterns.^{2,20} 2) SCCB arises from multipotent stem cells of the urinary bladder, which may explain not only the coexistence of mixed malignancies with SCC but also the heterogeneity of the immunohistochemical-staining pattern within SCC—the most widely accepted theory.^{2,12,18,22} 3) Urothelial metaplastic changes,⁸ such as intestinal metaplasia of bladder adenocarcinoma,^{18,22} and the presence of argyrophilic cells in many normal urologic tissues has supported the theory of derivation of SCCB from the amine precursor uptake and decarboxylation system,^{18,20} which is known to give rise to a variety of benign and malignant tumors such as adenomas, carcinoid-like tumors, apudomas, and carcinomas such as SCC.^{2,22} Ultrastructurally, these cells have intracytoplasmic dense-core neurosecretory granules, presumed to be the source of peptide-hormone secretion.²²

Pathology

SCCB, undifferentiated from other bladder tumors at cystoscopy, is usually a broadly based solid mass 2–10 cm in diameter, with an ulcerated or hemorrhagic surface with areas of necrosis,^{2,20,21} and most frequently

involves the lateral wall, dome, and posterior wall of the bladder.^{2,7,16,20}

The WHO has defined three groups of SCC based on light microscopic appearance: the oat cell type,^{2,25} the intermediate-cell type, and the combined carcinoma type. Approximately 40%^{1,8} of SCCB has a mixed tumor component with other histologic types of malignancy,^{2,19,22,23} most commonly transitional cell carcinoma (TCC), followed by adenocarcinoma and squamous cell carcinoma.^{2,4,12,22}

SCCB is characteristically distinguished by the presence of ultrastructural features, such as intracytoplasmic dense-core neurosecretory granules 30–300 nm in size, coarse chromatin in round to oval nuclei, inconspicuous nucleoli, sparse cytoplasmic organelles such as Golgi complex, and occasional mitochondria.^{2,4,13,19,20-22} SCCB is frequently associated with genomic alterations, the most common of which include deletions at 10q, 4q, 5q, 13q and DNA gains at 8q, 5p, 6p, and 20q.² Rearrangements of long arms of chromosomes 6, 9, 11, 13, and 18 with hypertriploid DNA and p53 expression have been demonstrated in patients with SCCB.¹⁶ Paraneoplastic syndromes are uncommon.^{4,7,8} SCCB tends to present as large tumor masses and invades deeply into the muscle layer early in its course.⁸

Immunohistochemistry

SCCB expresses a variety of markers, all nonspecific. These include neuroendocrine markers such as neuron-specific enolase (NSE), epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), and cytokeratin. Highly specific markers include chromogranin A and synaptophysin.² Although nonspecific, NSE is the most sensitive and most frequently expressed neural marker (90%),²⁵ and EMA is the most commonly expressed epithelial marker (62%).²² Hoque and associates defined aberrant DNA methylation in the urine and serum samples of renal, urethral, and retroperitoneal cancer patients with a high sensitivity and specificity.²⁶ Leukocyte common antigen (LCA) has been used to differentiate lymphoma from SCC, as LCA is commonly expressed in lymphoma but never in SCC.^{2,22} Higher expression of CHR, SYN, NSE, and other neuroendocrine markers, such as serotonin, have been frequently reported.^{2,10,12,13,16,22,23} Reactivity to NSE seems to be a consistent finding, whereas reactivity to CHR is weak and focal.⁴ In general, immunohistochemical expression of neuroendocrine markers in small cells has a poorer prognosis.^{2,12}

Thyroid transcription factor 1 (TTF-1), commonly expressed in pulmonary SCC,^{5,10} was found to be positive in 39% of SCCB cases in a review by Jones

and coauthors.⁵ There was no correlation between TTF-1 expression and survival. In addition, none of the clinicopathologic parameters—including age, gender, presenting symptoms, smoking history, pathologic T stage, lymph node or distant metastasis,⁵ the presence of coexisting non-SCC components,^{1,7,8,22} clinical stage,^{3,5} presence of neuroendocrine features,²⁰ chemotherapy or radiation therapy, or treatment with or without cystectomy²³—is associated with a significant survival difference.¹

Clinical Presentations

Painless gross hematuria is the most common presenting symptom in SCCB due to a large polypoid ulcerated and deeply invasive tumor.^{2,4,8,12-16,18-23} Dysuria and irritative symptoms have been reported as the second most common symptoms. Urinary frequency, urethral obstruction, and paraneoplastic syndromes with secretion of ectopic adrenocorticotropic hormone and Cushing syndrome have been reported occasionally.^{1,4,7,8,10,22,23} Swanson and colleagues reported no paraneoplastic syndrome or “carcinoid syndrome” in their case study.²⁷

The most common site of metastases is local or distant lymph nodes, followed by liver, bone, lung, brain, adrenal gland, spleen, and abdominal cavity.²² The occurrence of second bladder primary malignancy (eg, TCC of the bladder) has been reported as a complication of SCCB in surviving patients.¹⁴ Primary SCCB must be differentiated from lymphoma, malignant melanoma, neuroblastoma, embryonal rhabdomyosarcoma, Ewing sarcoma, carcinoid, and metastases from primary SCLC.²² LCA and cytokeratin markers have been used to differentiate SCCB from lymphoma.¹⁹

Diagnosis

Diagnosis of SCCB is most often accomplished via cystoscopy and transurethral biopsy. Focal necrosis and a moderate mitotic rate are common. Immunocytochemical staining is helpful if light microscopy is not definitive.¹⁶ A significant number of the patients with presumed localized disease actually have undiagnosed metastases at presentation,⁴ most commonly to liver, bone, extrapelvic lymph nodes, peritoneal cavity,^{8,10} the parailiac, paraortic, and supraclavicular lymph nodes; vertebral and costal bones; abdominal cavity; and brain.^{20,21} CT of the abdomen and pelvis, bone scan, and chest radiograph at the time of diagnosis of SCCB, and CT scan of the brain in the presence of neurologic signs or symptoms, are warranted.² Sensory neuropathy has been reported as an exceptional presentation of the SCCB, associated with the “antiHu” autoantibody (immunoglobulin G) against neuronal nucleoprotein antigens.¹²

Treatment

SCCB has a poor prognosis, which may be influenced only by the extent of disease at the time of diagnosis and the use of combination chemotherapy.⁸ Only cisplatin-based chemotherapy has been shown to influence survival.^{2,6,12} The optimal therapeutic strategy is still unknown, mainly because of the relative rarity of the tumor, which precludes prospective trials. It is apparent that surgery alone is associated with a high rate of recurrence, owing to micrometastases at the time of diagnosis.^{1,3-11,18,22,23,26} Siefker-Radtke and associates suggested that using four cycles of aggressive multiagent preoperative chemotherapy followed by radical cystectomy may be the optimal strategy.⁹ Other proposed methods of therapy include cystectomy with adjuvant chemotherapy, the combination of chemotherapy with transurethral resection, and partial cystectomy and radiotherapy. In patients with local disease, long-term remission and potential cure can be achieved by chemoradiotherapy, especially in those with small and confined tumors. This strategy could allow for preservation of the bladder in most patients.⁶ Survival improves in patients receiving additional platinum-based chemotherapy. The most important concern about using cisplatin is its nephrotoxicity; in addition, even simple chemotherapy schedules in elderly and frail patients could be very toxic.⁷ Choong and coauthors recommended radical cystectomy in all patients with SCCB plus systemic platinum-based chemotherapy in metastatic disease.⁸ Grignon and colleagues recommended the use of aggressive surgery in combination with adjuvant multidrug chemotherapy, administering methotrexate, vinblastine, doxorubicin, and cisplatin for mixed tumors and doxorubicin, etoposide, and cisplatin for pure SCCB.¹⁹ Chemotherapy with local radiotherapy in patients with limited-stage SCCB, and preoperative chemotherapy have resulted in a markedly improved survival.⁸

Cystectomy is not the treatment of choice for those with limited disease. Chemotherapy is not feasible in more than one half of the elderly patients with significant comorbidities who have limited disease. Only 30% of patients with SCCB were observed to have extensive disease at presentation in comparison with 60–70% in patients with SCLC.⁶

Karpman and associates reported that primary chemoradiotherapy is an attractive option because of the known sensitivity of this type of tumor to both chemotherapy and radiotherapy.¹¹ Additionally, chemoradiotherapy provides a high probability of preserving the native bladder.

Abbas and coauthors suggested that the best disease-free survival was achieved when the primary tumor

was resected followed by combination chemotherapy.²² Radiotherapy, when used in combination with multidrug chemotherapy and/or surgical treatment, has produced some long-term survivors.

Prognosis

The prognosis of SCCB is poor^{1-10,12-17,22,23,26} and is poorer still in the setting of metastatic disease.³ Only four cases with localized disease at diagnosis have been reported to have survival exceeding 5 years.^{4,22} The prognosis for SCC has been shown to be partially dependent on the primary disease site.⁵ There is a high propensity for metastatic spread and early death by SCCB.⁷ The overall 5-year survival rate is only 8%,^{1,7,8,14} whereas the overall mean survival is 9.8 months and overall median survival is between 4.0 and 7.3 months.

Elevated creatinine or unilateral ureteric obstruction indirectly causes poor prognosis by precluding the use of cisplatin-based chemotherapy. Therefore, cisplatin doses should be modified according to the rate of creatinine clearance.¹⁴ Elevated lactate dehydrogenase seems to predict for disease recurrence and death in SCCB. Continued periodic cystoscopic surveillance, with random biopsies in the absence of obvious mucosal abnormalities every 3 months for a minimum of 3 years after treatment, has been emphasized. An attempt should be made to reverse renal dysfunction from ureteric obstruction with percutaneous nephrostomy.¹⁴

Conclusion

Primary and pure SCCB occurs at several sites along the urinary tract, most frequently at the bladder. Bladder metastases from SCLC have rarely been reported in association with widely disseminated disease.⁷

SCCB is a very rare and aggressive tumor, and there is no commonly agreed-upon treatment protocol.⁷ Surgery alone is associated with a high rate of recurrence and comorbidities.^{6,9} Treatment schemes may be derived from the analogy with SCLC. Most case reports and small studies have recommended platinum-based chemotherapy followed by bladder radiotherapy, in suitable patients.⁷ An attempt should be made to reverse renal dysfunction from ureteric obstruction with percutaneous nephrostomy.¹⁴ An associated paraneoplastic syndrome is an uncommon complication, and an unusually aggressive behavior by a "bladder" cancer should alert the physician to the possibility of an SCC. These cases should be aggressively treated with a multimodality approach to gain some survival advantage.²² SCCB has a poor prognosis,^{2,6,12} with an overall survival from the time of diagnosis of between 2 and 21 months.¹⁹

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Review

Treatment of Small Cell Carcinoma of the Urinary Bladder: Can We Learn from Small Cell Lung Cancer?

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Agheli and colleagues present the case of a 58-year-old man with a bulky pelvic mass originating from SCCB.¹ The patient was treated with 10 courses of carboplatin and etoposide followed by external radiotherapy, with the mass responding partially, showing a reduction from 21 cm to 7 cm. After 18 months' follow-up, the patient developed brain metastases, from which he finally died, though the pelvic mass remained stable.

This case illustrates once again the poor prognosis of SCCB. Only platinum-based chemotherapy has been associated with significantly improved survival.²⁻⁴ Local therapy often fails due to micrometastases at diagnosis, but cases have been reported in which locally confined disease was curable.⁵ Often the bladder tumor is large, though the bulky pelvic mass presented in this case is exceptional. Evidence from the literature supports the postulation that the presence of SCCB in combined bladder tumors is the leading prognosticator^{2,4,6} and that it should be managed like pure SCCB. The low incidence of SCCB has until now precluded prospective randomized trials, and the optimal therapeutic strategy is still unknown. Cystectomy with neoadjuvant and adjuvant chemotherapy has been propagated^{4,6} as well as combinations of chemotherapy with transurethral resection, partial cystectomy, and radiotherapy.^{5,7} In contrast, SCLC, which shares many clinicopathologic features with SCCB, is far more common. A clinically relevant two-stage system of limited and extensive disease is widely used to determine prognosis and treatment of SCLC, and a consensus of combination chemotherapy and radiotherapy has emerged, depending on the extent of the disease.⁸⁻¹⁰

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Data demonstrate a similarity in the clinical course of SCCB and SCLC.¹¹ In SCLC, survival increased only after the introduction of polychemotherapy regimens. Most of the benefit occurred in patients younger than 65 years of age.¹² The definition of limited SCLC takes early metastasis into account, with tumor confined to the hemithorax, the mediastinum, or the supraclavicular lymph nodes of origin. All patients with tumor beyond these confinements have extensive disease. The current treatment of limited SCLC comprises a combination of cisplatin and etoposide plus chest irradiation, preferably during the first or second cycle of chemotherapy.^{10,13} A prophylactic cranial radiation follows in patients with a complete response. This strategy may result in median survival of 18–24 months and a 50% 2-year survival.¹⁴ Due to early micrometastasis, the overall survival of SCLC remains poor, with 5–10% survival after 5 years.¹⁵

The patient in the case reported by Agheli and associates developed a brain metastasis, though my observation is that brain metastases are less common in SCCB than in SCLC. My colleagues and I did not perform prophylactic cranial irradiation, and only 2 of 42 patients in our collective database died of a brain metastasis.

SCCB is usually staged according to the Tumor, Node, Metastasis classification, which fails with regard to micrometastases. In the largest retrospective analysis of SCCB, tumor stage was not independently associated with survival, suggesting that micrometastases are often present in clinically localized disease.² Because of the clinicopathologic similarities between both tumor sites and the simplicity of the two-stage system and its clinical relevance for treatment decisions, we proposed to define both limited and extensive SCCB as analogous to SCLC. To account for the presence of micrometastasis, limited SCCB, like limited SCLC, would not differentiate between locoregional N0 and N1 disease. Extensive SCCB would require larger lymph nodes or distant metastases. Other centers have reported a similar staging approach.¹⁶ Due to the dismal prognosis of SCCB, an organ-sparing treatment strategy of chemotherapy and radiotherapy, similar to its pulmonary counterpart, which depends on a simple two-stage system, is an attractive concept.

As the authors of the present case report point out, there is evidence that systemic chemotherapy is the most important factor influencing survival in limited SCCB and that the choice for cystectomy or radiotherapy as local consolidating treatment may be a lesser influence on survival. In recent years, several larger series reported experience with cystectomy for limited SCCB with either neoadjuvant or adjuvant chemotherapy,^{4,17} but only a few centers offered a bladder-sparing approach with sequential chemoradiation.¹⁸⁻²⁰ At present, we have performed sequential chemoradiation for limited SCCB in 17

patients, of whom 47% developed systemic progression after a median time of 6 months, indicative of the aggressive nature of the disease. Though 5-year survival times following bladder-sparing with chemoradiation have been reported in a small case series,²⁰ this approach has been criticized for the relatively high rate of local recurrence. Local recurrence rates of 20–69% have been reported^{18,20} in small series of 5 and 8 patients, respectively. In our experience, 23.5% of the patients developed a local recurrence, though histology revealed a transitional cell carcinoma in 3 of the 4 patients. The late recurrences after 43 and 50 months indicate that long-term follow-up by cystoscopy is necessary.

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diagnostics are ordered only once in a person's lifetime but may have implications for the treatment of other cancers and medical illnesses. The willingness to pay for these tests by any individual insurance company may not reflect their aggregate social value across all health benefits or any potential cost savings, given the fractured coverage system of the United States. Like iOWH, a firm could enter the pharmacogenomic diagnostic development process at the point at which for-profit firms find it unprofitable to continue R&D or when academic researchers have found no willing government or for-profit firm to partner with for further investment.

Scientific and business leadership could be marshaled toward this purpose. There are many individuals in the for-profit industry and academia with significant expertise in clinical therapeutics and pharmacology and a commitment to translational oncology product development. The public is rich with individuals with a deep personal commitment to finding effective cancer therapies. Almost one sixth of health philanthropy in the United States is devoted to cancer research; consequently funding for a cancer-based nonprofit biotechnology firm maybe relatively easy to raise.

In sum, a nonprofit oncology biotechnology firm would allow for the leveraging of existing investment in the early stages of R&D by for-profit companies and academia, provide an infrastructure for technology transfer for these partners, and provide private donors the unique opportunity to commit directly to translational R&D (in contrast to existing cancer charities), with the goal of serving the public's interest. Ultimately, this focus would establish proof of principle for the establishment of nonprofit biopharmaceutical firms focused on other socially important, but neglected, areas for investment by for-profit firms in the future.

Suggested Readings

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