Background

The urokinase plasminogen activator (uPA) system is thought to play a role in several different processes important to tumor progression including angiogenesis (1), tumor growth (2), and metastasis (3). This system is composed of a serine protease (uPA), its glycolipid (glycosylphosphatidylinositol) anchored receptor (uPAR), and several serine protease inhibitors (serpins) including plasminogen activator inhibitors 1 and 2 (PAI-1 and PAI-2; ref. 4). uPA can bind to uPAR leading to the subsequent activation of plasminogen to plasmin (5). Plasmin is a promiscuous protease that initiates several extracellular proteolytic cascades, which will be discussed in detail later in this review. The binding of uPA to uPAR increases the efficiency of plasminogen activation (5) and also serves to localize these proteolytic cascades to the migrating or invading edge of cells (6). This proteolysis is tightly controlled by PAI-1 and PAI-2, and the PAI-uPA-uPAR complex can be internalized with uPAR being recycled to the cell surface (7). The importance of this system in tumor progression is not a recent revelation, and in fact, data supporting an integral role for the uPA system in tumor progression have been accumulating in the literature for >30 years. However, despite this wealth of data, the therapeutic targeting of the uPA system has remained an elusive objective. uPA, uPAR, and PAI-1 can all potentially be targeted for cancer therapy and there is an entire literature surrounding the targeting of uPA and PAI-1, which will not be discussed in this review. Rather, this review will focus on the therapeutic targeting of uPAR and will present a historical perspective on targeting this receptor and how a paradigm shift in the understanding of uPAR behavior on the cell surface has created novel opportunities to develop therapeutic agents to target this receptor. Finally, this review will summarize therapeutic approaches that have been attempted and will describe new approaches that are currently in development with the goal of advancing the first uPAR-targeted therapy into clinical trials.

Expression in cancer. uPAR is expressed in most solid and several hematologic malignancies, which are summarized in Table 1. One of the reasons that uPAR is such an attractive target is that its expression is restricted quite tightly to tumor tissue and it is rarely expressed in adjacent normal tissue (8, 9). However, uPAR expression may be up-regulated on certain cells during pathologic processes such as during wound healing and inflammatory response to infection (10, 11). uPAR is expressed in tumors by multiple tumor-associated cell types including the tumor cells themselves, endothelial cells, stromal cells, and infiltrating inflammatory cells such as neutrophils and macrophages. uPAR expression is also up-regulated by hypoxia and may facilitate the epithelial-mesenchymal transition hypothesized to occur as a tumor acquires an invasive phenotype (12). Tumors that express uPAR generally fall into two categories: those that express uPAR on both tumor and tumor-associated cells [e.g., pancreatic cancer (13), bladder cancer (14), and renal cell carcinoma (9)] and those that do not express uPAR on the tumor cells but do express uPAR on the tumor-associated cells [e.g., colon (15), breast (16), and prostate (17) cancer]. The role of uPAR expressed on tumor-associated cells has been somewhat controversial, but it is now well accepted that angiogenic endothelium in a tumor is required for tumor growth and it is becoming increasingly clearer that the presence of tumor-associated inflammatory cells is often correlated with poor...
prognosis (18) and can further contribute to tumor progression (19). This emphasizes the importance of targeting these tumor compartments in addition to targeting tumor cells themselves. To that end, uPAR expression is up-regulated on neutrophils and macrophages associated with a tumor compared with their normal counterparts circulating in the blood or residing within normal tissue (20). uPAR expression is also observed on angiogenic endothelium (21) within a tumor as well as on other tumor stromal cells (22) and a recent study in patients with breast cancer has correlated uPAR expression in tumor-associated stromal and inflammatory cells with poor prognosis (23).

When uPAR is expressed by tumor cells, it is often not expressed uniformly in all tumor cells within the tumor and is usually restricted to cells at the invasive edge of a tumor or in tumor cells at the tumor-stromal interface (24). This pattern of expression has led to the hypothesis that uPAR may be one of several tumor stem cell antigens and several reports have appeared recently supporting this hypothesis (25, 26). In addition, uPAR expression appears to increase with grade or stage of the tumor and may be enriched in metastatic lesions (27). Taken together, these data provide strong circumstantial evidence that targeting uPAR will lead to the simultaneous treatment of several tumor-associated cell types that are important to tumor growth and provide a strong rationale for the development of anti-uPAR therapeutics.

### Role of uPAR in mediating cell surface proteolysis

The function of the uPA system has classically been thought to be the regulation of plasminogen activation and extracellular proteolysis (Fig. 1A). uPA is secreted as a single-chain zymogen, pro-uPA or single-chain uPA (scuPA), which must be activated to its two-chain active form, uPA (28). Plasmin (the activated form of plasminogen) has been hypothesized to activate scuPA, but this was difficult to reconcile because plasmin is also secreted as a zymogen, plasminogen (that also requires activation), which raised the issue of which enzyme is activated first and how. Other proteases such as kallikreins and cathepsins that were capable of activating scuPA in vitro have also been proposed for the first activation event that then led to subsequent plasminogen activation, but these proteases are less catalytically efficient activators of scuPA than plasmin and it was unlikely that they would functions in this capacity in vivo. Recently, a membrane-bound protease, matriptase, was shown to activate scuPA with high catalytic efficiency on leukocytes (29). Although matriptase is also expressed as a zymogen, it is capable of autoactivation and is thus a compelling candidate for the initiator of the plasmin cascade through the activation of scuPA to uPA.

Alternatively, the binding of scuPA to uPA has been shown to activate plasminogen to plasmin in the absence of converting scuPA to uPA in vitro (30), and it has been suggested that the binding of scuPA to uPAR induces a conformational change in scuPA in the absence of conversion to two-chain uPA that allows it to activate plasminogen to plasmin. Regardless of which mechanism is operative in vivo, uPA bound to uPAR activates plasminogen (which also binds to several cell surface proteins) ~50-fold more efficiently than if both molecules were free in solution; thus, one of the roles of uPAR in this extracellular proteolytic cascade is to increase the efficiency of plasminogen activation (3). Once plasminogen is activated to plasmin, an entire series of downstream reactions can be initiated. During normal hemostasis, the role of plasmin role is to lyse fibrin clots. However, in a tumor milieu, in addition to fibrinolysis, plasmin is able to proteolyze extracellular matrix (ECM) components and release ECM-bound growth factors such as vascular endothelial growth factor and basic fibroblast growth factor either directly (31) or indirectly (32) through the activation of pro-matrix metalloproteinases, which when activated can also further degrade ECM.

In addition to making plasminogen activation by uPA more efficient, uPAR also imparts directionality to the proteolytic process. Because uPA is glycosylphosphatidylidylositol anchored to the outer plasma membrane, it has been hypothesized to redistribute to the invasive or migrating front of a cell thereby focusing proteolysis in the direction of movement, creating a path through the ECM as well as creating

### Table 1. Tumor types expressing uPAR

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Observation</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Breast</td>
<td>High incidence of immunostaining; expression correlates with poor prognosis</td>
<td>16, 23</td>
</tr>
<tr>
<td>Acute myeloid leukemia,</td>
<td>Decreasing plasma single-chain uPAR</td>
<td>74</td>
</tr>
<tr>
<td>acute lymphocytic leukemia</td>
<td>correlates with decreasing circulating tumor cells in response to treatment</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>Expressed in tumor cells in late-stage disease</td>
<td>75</td>
</tr>
<tr>
<td>Prostate</td>
<td>High prevalence in late-stage disease; increased expression in metastases and Gleason score &gt;7</td>
<td>17, 76</td>
</tr>
<tr>
<td>Ovarian</td>
<td>Soluble uPAR may be an indicator of effectiveness for chemotherapy</td>
<td>77</td>
</tr>
<tr>
<td>Bladder</td>
<td>High prevalence; increased expression with stage and grade</td>
<td>14</td>
</tr>
<tr>
<td>Renal cell</td>
<td>High prevalence; increased expression with stage and grade</td>
<td>9</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>High prevalence of expression</td>
<td>13</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Higher expression in follicular and anaplastic thyroid cancer</td>
<td>78</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>High prevalence associated with invasive growth</td>
<td>79</td>
</tr>
<tr>
<td>Gastric</td>
<td>Only one-third tumors positive</td>
<td>80</td>
</tr>
<tr>
<td>Glioma</td>
<td>Increased expression in high-grade tumors in tumor and endothelial cells</td>
<td>21</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>Higher expression in tumor than in normal tissue does not correlate with survival</td>
<td>81</td>
</tr>
<tr>
<td>Colon</td>
<td>Strong immunostaining of infiltrating cells at the invasive front</td>
<td>15</td>
</tr>
<tr>
<td>Myeloma</td>
<td>Soluble uPAR correlates with extra-bone marrow involvement and poor prognosis</td>
<td>82</td>
</tr>
</tbody>
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a gradient for movement by generating chemotactic ECM fragments and freeing growth factors (6). Based on these observations, early hypotheses on how to target this system therapeutically centered around the inhibition of plasminogen activation either by targeting the catalytic activity of uPA directly, which could be done with a small molecule, for example, or by attempting to block scuPA or uPA binding to uPAR (Fig. 1A). The latter was a more challenging drug discovery problem due to the much larger surface area, compared with an enzyme active site, which would need to be targeted to block a protein-protein interaction (e.g., uPA-uPAR). Several proof-of-principle studies aimed at disrupting uPA-mediated proteolysis using small-molecule inhibitors of uPA (33), peptide inhibitors of the uPA-uPAR interaction (34), and antibody-like inhibitors (35) have been published, but for the most part the results have been disappointing with modest effects observed on tumor growth and metastasis. One of the problems in evaluating many of these agents and especially the ones that attempt to interfere with uPA binding to uPAR is that the interaction of uPA with uPAR is highly species specific such that mouse uPA does not bind to human uPAR and vice versa. Thus, in a typical tumor xenograft model where the tumor cells were of human origin and the host was mouse, only direct antitumor cell effects could be observed. In xenograft studies where molecules that could bind to mouse uPAR within the tumor were evaluated, the effects on tumor growth were

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**Fig. 1.** A, schematic representation of the “classic” role of uPAR in tumor biology. The ligand for uPAR, uPA, is a serine protease that mediates the activation of plasminogen to plasmin and this process occurs with greater catalytic efficiency when both molecules are bound to the cell surface (5). Once activated, plasmin unleashes several cascades leading to the degradation of ECM, the activation of pro-matrix metalloproteinases, and the activation and release of growth factors such as vascular endothelial growth factor that are deposited in the ECM (33–35). B, schematic representation of the role of uPAR in cell signaling. uPAR, despite being a glycosylphosphatidylinositol-anchored receptor and lacking a transmembrane domain, is capable of transmitting an intracellular signal. uPAR has several ligands/adaptors such as integrins that it associated with to form dynamic signaling complexes on the cell surface. The interactions with these non-uPA ligands may represent novel opportunities for the therapeutic targeting of uPAR (arrows).
significantly better (36). These studies further show the importance of targeting uPAR on tumor-associated cells, but unfortunately the development of a therapeutic targeting human uPAR would likely not bind to mouse uPAR, creating a challenge to the evaluation of human uPAR-targeted agents in mouse models. However, recent data using antisense approaches in human glioma tumor cells showed that decreasing uPAR expression in these tumor cells could have profound effects on tumor cell growth, survival and apoptosis, and invasion (37, 38). Thus, even by targeting only the tumor cell in a xenograft model, decreasing uPAR function could lead to robust antitumor activity, and despite limitations, uPAR-targeted therapies could still be evaluated in xenograft models with the presumption that any antitumor activity observed would be increased once these treatments were evaluated in humans. The disconnect between the antisense data and the data obtained using molecules that blocked the uPA-uPAR interaction or uPA enzymatic activity on a tumor cell suggest that, in addition to targeting the uPA-uPAR interaction, targeting other aspects of uPAR function should be considered.

Paradigm shift from extracellular proteolysis to intracellular signaling. It has become apparent over the past decade that the interaction of uPAR with uPA represents only one of several uPAR-ligand interactions. Much of this work arose from the observations that, despite being a glycosylphosphatidylinositol-anchored receptor with no transmembrane domain, uPAR was capable of mediating intracellular signaling. It is now apparent that uPAR can exist in dynamic signaling complexes on the cell surface that may include integrins (39), epidermal growth factor receptor (40), platelet-derived growth factor receptor (41), the internalizing receptor lipoprotein receptor-related protein (42), caveolin (43), vitronectin (44), and possibly other cellular components (Fig. 1B). uPAR may interact with these proteins and the pathways that they mediate either directly or indirectly. For example, a direct association of uPAR with αβ1 has been described and a 9–amino acid peptide composed of amino acids 240–248 of uPAR can directly bind to αβ1 (45).

Substitution of a single amino acid within this region by alanine (S245A) in cell surface–expressed uPAR impaired its interaction with αβ1. Direct interactions of uPAR with αβ1 (46), αβ1, αβ1, αβ1, αβ1 (47), and Mac-1 (48) have also been reported in a variety of cell types including tumor cells and monocytes/macrophages. uPAR-integrin interactions stimulate intracellular signaling via SRC (49, 50) and the activation of focal adhesion kinase (51) leading to alterations in matrix assembly and proliferation and the induction of tumor cell dormancy. uPAR may also interact directly with proteins such as lipoprotein receptor-related protein (52), platelet-derived growth factor receptor (41), the G-protein-coupled receptor FPRL-1, a homologue to the fMLP receptor (53), and vitronectin (44). uPAR can also have indirect effects on various signaling pathways. For example, uPAR is required in order for epidermal growth factor receptor to transmit a mitogenic signal in response to epidermal growth factor, a process that is dependent on SRC (49). There is also recent evidence that suggests that, in some processes such as matrix assembly (50) or epidermal growth factor–mediated migration, ternary complexes of uPAR-integrin-epidermal growth factor receptor may be involved (54).

Experiments using uPAR knockdown approaches also show profound effects on uPAR signaling and tumor cell phenotype. The down-regulation of uPA and uPAR expression using RNA interference in SNB19 human glioma cells inhibited both RAS- and MEK-mediated signaling, affecting the activation of several potential cancer targets including extracellular signal-regulated kinase 1/2, phosphatidylinositol 3-kinase, p38, and c-Jun NH2-terminal kinase and promoted apoptosis in vitro (55). Anti-uPAR antisense also inhibited tumor cell invasiveness and proliferation of melanoma cells in vitro and tumor growth and metastasis in vivo (56). These observations suggest that targeting uPAR signaling has the potential to affect multiple tumor-promoting pathways in parallel, leading to robust antitumor effects and providing an alternative therapeutic strategy to targeting the proteolytic aspects of uPAR. Taken together, the data support the hypothesis that targeting the dynamic interactions of uPAR in mediating cell signaling might lead to novel anti-uPAR-targeted therapeutics for the treatment of cancer.

Clinical-Translational Advances

Several peptidic and small-molecule inhibitors of uPA binding to uPAR have been described in the scientific and patent literature. Cyclic peptide inhibitors based on the growth factor domain (GFD) of uPA and cyclized using non-disulfide-based linkers were reported in the patent literature (57) and described to have anti-invasive activity in vitro (58). A pegylated human GFD (amino acids 1-48 of uPA), which would be expected to compete uPA binding to uPAR, had modest effects on survival when used alone in a U87MG glioma xenograft model (36). However, a pegylated mouse GFD had a substantially greater effect on survival in this study, and this effect was enhanced when the human and mouse GFD were combined, again emphasizing the importance of targeting the host-derived stromal tissue to inhibiting tumor growth. Disulfide cyclized GFD-derived peptides (composed of amino acids 19-31 of uPA)-DOTA conjugates bound to 213-Bi (an α-emitter) were shown to be cytotoxic to OV-MZ-6 uPAR-expressing ovarian cancer cells in vitro and localized to these cells when they were injected i.p. in mice (59). Multifunctional inhibitors containing peptides derived from the GFD, the NH2-terminal domain of TIMP-1 or TIMP-3 (matrix metalloproteinase inhibitors) and cystatin (a cysteine protease inhibitor) have also been described and shown to inhibit the growth and invasion of ovarian cancer cells in vivo (60).

Several linear peptide approaches have also been described. Over a decade ago, Kobayashi et al. showed that a linear peptide derived from the GFD could inhibit the invasion and metastasis of 3LL cells (34). Recently, peptides with some homology to the uPAR-binding region of uPA were discovered via phage display and further optimized using combinatorial approaches (61). This resulted in a set of peptides containing D isomer and nonnatural amino acids that bound to human uPAR with high affinity (Kd < 1 nmol/L). Several of these (AE120 and AE 152) were shown to inhibit HEP3 carcinoma cell intravasation in a chick chorioallantoic membrane model (61). Peptides derived from integrins that block uPAR-integrin interactions have also been described. M25, a peptide derived from the β2 subunit of Mac-1, inhibited leukocyte adhesion to fibrinogen, vitronectin, and cytokine-stimulated endothelial cells. M25 also blocked the association of uPAR with β2 and impaired β2-integrin-dependent spreading and migration of...
human vascular smooth muscle cells on fibronectin and collagen (62). A second peptide that inhibits uPAR-integrin complex formation, P25, was able to decrease tumor cell attachment to vitronectin and increase tumor cell attachment to fibronectin (63). P25 administered using osmotic minipumps also inhibited the experimental metastasis of MDA-MB-231 cells to bone (63).

Several small-molecule inhibitors of the uPA-uPAR interaction have also been reported. Glycaminide inhibitors with double digit nanomolar potency in uPA-binding assays have been described but never evaluated in functional assays or animal models (64). Similarly, oligothiophene derivatives that inhibit uPA binding to uPAR with IC$_{50}$ values in the micromolar range (65), O-substituted hydroxycumaranes, which are claimed to inhibit uPA binding to uPAR with IC$_{50}$ values of 0.05 µg/mL (66), and substituted aminobiphenyl-carboxylic acid derivatives, the most potent of which is claimed to inhibit the binding of uPA to uPAR with an IC$_{50}$ value of 0.8 nmol/L, have been described in the patent literature (67). Biological data evaluating these compounds have ever been published, and unfortunately, as with the peptide approaches targeting uPAR, none of these small molecules have advanced into preclinical development or clinical studies.

There has also been substantial recent interest in targeting uPAR using monoclonal antibodies. In a proof-of-principle study, Rabbani and Gladu showed that a polyclonal rat IgG targeting the NH$_2$ terminus of rat uPAR could inhibit tumor growth and lead to regressions in a syngeneic rat breast cancer model using Mat BIII cells (68). In that study, significant apoptosis as well as inhibition of invasion were noted in the tumors. Because these were immunocompetent animals and the antibody was also of rat origin, it was possible that antibody-dependent cell-mediated cytoxicity could have contributed to the observed antitumor effects. Despite this promising result, there has been very little activity in developing an antibody therapeutic targeting uPAR until recently. Fully human monoclonal antibodies that block uPA binding to uPAR have recently been described (69). These antibodies inhibit tumor cell invasion in vitro and tumor growth by 25% to 50% in vivo and affect uPAR-dependent signaling by down-regulating extracellular signal-regulated kinase and focal adhesion kinase phosphorylation in tumors grown in vivo. A modest effect on tumor cell proliferation and angiogenesis is also observed. Another antibody, ATN-658, which does not inhibit uPA binding to uPAR, has shown significant antitumor activity in several orthotopic animal tumor models. ATN-658 inhibited the growth, invasion, and metastasis of the pancreatic carcinoma cell line L3.6pl and was able to enhance the antitumor activity of the positive control, gemcitabine, in that study (70). One unexpected observation from that study was that ATN-658 monotherapy was able to significantly inhibit ( ~ 70%) tumor cell proliferation. ATN-658 is specific for human uPAR and does not cross-react with nonhuman uPAR. Thus, this antiproliferative activity was likely due to a direct antagonistic effect on the xenografted tumor cells because this antibody is not able to mediate antibody-dependent cell-mediated cytotoxicity in mice (the lack of cross-reactivity of ATN-658 for nonhuman uPAR also suggests that the antitumor activity of this antibody may be underrepresented in xenograft studies). ATN-658 also inhibited the growth of several ovarian cancer cell lines inoculated i.p. Similar to the pancreatic cancer study, the magnitude of the antitumor activity of ATN-658 monotherapy was similar to the positive control, paclitaxel, and an enhancement of antitumor activity was observed when the two agents were combined (71). In a model of colon cancer metastasis, where the human colon carcinoma cell line HCT-116 is inoculated directly into the liver, ATN-658 inhibited tumor growth regardless of whether treatment was started when tumor burden was low (day 4) or high (day 11, average tumor volume in a satellite group of animals was >400 mm$^3$; ref. 72). The antitumor effect was more pronounced in the animals with high tumor burden where ATN-658 inhibited tumor growth by ~ 85%. Finally, ATN-658 inhibited PC-3 cell growth in the tibia in a model of prostate cancer metastasis (73). Focal adhesion kinase and AKT activation were also significantly inhibited in tumors from the ATN-658-treated mice. ATN-658 has been humanized and is currently in preclinical development with an Investigational New Drug filing anticipated in early 2009.

### Conclusion

There is a large body of published evidence that suggests that targeting uPAR could have broad-spectrum antitumor effects. Although this target has been known for many years, attempts at developing a therapeutic targeting uPAR have never advanced past the in vivo proof-of-principle stage. However, recent data describe several monoclonal antibodies that have the potential to enter the clinic in the near future. It may finally be the right time to evaluate the hypothesis that uPAR plays a major role in tumor progression and that targeting uPAR will lead to clinical benefit in cancer patients.

### Disclosure of Potential Conflicts of Interest

P. Mazar is employed by and holds patents with Attenuon, LLC.

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Urokinase Plasminogen Activator Receptor Choreographs
Multiple Ligand Interactions: Implications for Tumor
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Andrew P. Mazar


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