Lighting up cancer aggressiveness: targeting the urokinase plasminogen activator receptor for intraoperative optical imaging
Baart, V.M.

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Chapter 6

A multimodal molecular imaging approach targeting uPAR for the diagnosis, resection, and surveillance of urothelial cell carcinoma


Abstract

With a 5-year recurrence rate of 30-78%, urothelial cell carcinoma (UCC) rates amongst the highest of all solid malignancies. Consequently, after transurethral resection patients are subjugated to life-long endoscopic surveillance. A multimodal near-infrared (NIR) fluorescence based imaging strategy can improve diagnosis, resection, and surveillance, hence increasing quality of life.

Methods & Results: Per immunohistochemistry, UCCs show prominent uPAR expression at the tumor-stroma interface and EpCAM on epithelial cells. uPAR and EpCAM are expressed by 6/7 and 4/7 UCC cell lines, respectively. In vitro, MNPR-101-IRDye800CW has a picomolar affinity for domain 2-3 of uPAR. In vivo fluorescence imaging with MNPR-101-IRDye800CW, specifically delineates both subcutaneous and orthotopic human UM-UC-3luc2 tumors with TBRs reaching as high as 6.8, differing significantly from the isotype controls Infliximab-IRDye800CW and Rituximab-IRDye800CW ($p < 0.0001$). Photoacoustic 3D in depth imaging confirms the homogenous distribution of MNPR-101-IRDye800CW through the tumor.

Conclusion: MNPR-101-IRDye800CW is suitable for multimodal imaging of UCC, awaiting clinical translation.
Introduction

Despite advances in detection, treatment, and surveillance of urothelial cell carcinoma (UCC) there has been no major improvement in overall prognosis over the past 30 years, with nearly 200,000 patients still succumbing annually [1, 2]. Clinically, UCC represents two sequential entities: non-muscle invasive bladder cancer (NMIBC), where malignant cells are constrained to the epithelial layer, and muscle-invasive bladder cancer (MIBC) wherein the tumor invades surrounding subepithelial tissue [3]. The majority of UCC cases (75-85%) are NMIBC and are marked by a high 5-year recurrence rate of 30-78% and 7-40% chance of progression to MIBC disease after transurethral resection (TUR). Therefore, NMIBC requires intensive surveillance via cystoscopy [4, 5]. Once UCC progresses, definitive therapy, defined as radical cystectomy with or without (neo) adjuvant therapy, is indicated [3]. Hereof, 6.3% show involved margins with significantly reduced recurrence-free and cancer specific survival [6]. Consequentially, UCC causes a high burden of disease, where patients could benefit from improved TUR and tumor free resection margins.

Real-time intraoperative guidance with near-infrared (NIR) fluorescence tracers has the potential to function as an extra sense, not only informing surgeons about tumor localization during resection, but also about the degree of disease-aggresiveness [7]. Fundamental for successful imaging is the identification of appropriate cancer-specific targets [8]. Ideally, a single target overexpressed in all patients (across multiple tumor types) is identified. Currently no such target exists. Epithelial cell adhesion molecule (EpCAM) is one of the most promising pan-tumor targets, found to be over-expressed in most solid tumor types and is clinically being evaluated in NIR imaging studies (NL7363). UCC’s, however, do not universally express EpCAM; 56% of UCCs are EpCAM negative and the overexpression rate compared to healthy tissue is 27% [9]. Hence, EpCAM-based tracers will not be applicable for all UCC patients, requiring the search for alternative targets with complementary expression patterns.

An alternative candidate for UCC targeting is the urokinase plasminogen activator receptor (uPAR). uPAR narrowly orchestrates various tumor specific processes, including cell differentiation, proliferation, and migration, but is barely present in healthy tissues. Immunohistochemical localization of uPAR on 186 human UCC specimen revealed expression of this receptor in 96% of the tumors, particularly at the invasive front, irrespective of grade and stage, while being completely absent in normal bladder [10]. Such a pattern is ideal for molecular imaging [11]. Recent preclinical studies confirmed the applicability of mouse anti-uPAR antibodies conjugated to the fluorophore ZW800-1 for optical imaging of oral and colorectal
cancer [12, 13]. However, the use of an alternative fluorophore, IRDye800CW (800F), offers the possibility of imaging via NIR light, as well as via photoacoustic (PA) imaging [8, 14]. PA imaging utilizes the contrast of optical imaging with the spatial resolution of ultrasound, enabling a tissue penetration depth of several centimeters [14, 15]. In the clinic, a bimodal tracer, capable of both optical NIR- and PA-imaging, can be utilized during non-invasive (trans-abdominal) surveillance, TURs and radical cystectomies.

In this study we developed a humanized NIR molecular imaging tracer for simultaneous fluorescence and PA-imaging to facilitate resection of human UCC in a clinically relevant mouse model.

**Materials and methods**

*Human samples and immunohistochemistry*

Formalin-fixed, paraffin-embedded tissue blocks of fourteen patients who underwent cystectomy or TUR for UCC were collected from the Department of Pathology of the Leiden University Medical Centre (LUMC). Sections of 4 µm were stained according to standard immunohistochemical methods as described in Appendix A. Sections were digitalized using the Panoramic Digital Slide Scanner, viewed with Caseviewer 2.3 (both 3D Hitech, Hungary) and scored for percentage of positive cells and staining intensity with the total-immunostaining score (TIS). TIS > 4 was defined as overexpression [16]. The LUMC ethics review board approved the study protocol (B20.030). Samples and data were non-identifiable and used in accordance with the 1964 Helsinki declaration.

*In silico analysis of gene expression in a TCGA dataset*

The freely available raw TCGA (The Cancer Genome Atlas) transcriptome database, consisting of bladder urothelial carcinoma samples (http://www.cbioportal.org/study?id=blca_tcg) was used to determine the correlation between the gene expression of EpCAM and uPAR/PLAUR in a mostly non-chemo treated MIBC cohort of 408 patients.

*Cells*

Suppliers and culture conditions of the UCC cell lines UM-UC-3, J82, T24, RT112, RT4, HT-1197 and HT-1376, and the transfected cell lines HEK EV (empty vector), HEK uPAR wildtype (WT) and the cleaved isoform HEK uPAR D2-3 are described in Appendix B. Further characterization of the UCC cells according to patient
characteristics and molecular profile can be found in Appendix C.1-2. Cell lines were routinely tested for mycoplasma.

**Antibodies**

ATN658 is an extensively validated mouse monoclonal antibody of the IgG1 κ isotype targeting domain 3 of uPAR [12, 13]. MNPR-101 (formerly known as huATN658) is the humanized variant. Both antibodies are not cross-reactive with mouse uPAR [17]. Rituximab and Infliximab (Remicade®) are clinical grade chimeric human-mouse antibodies, consisting of the glycosylated human IgG1 κ isotype constant domain, targeting CD20 and tumor necrosis factor-α (TNFα), respectively.

**Surface Plasmon Resonance**

Binding of ATN658 and MNPR-101(-800F) to recombinant human uPAR (10925-H08H, Sinobiological, China) was measured by surface plasmon resonance on a Biacore T200 instrument (GE Healthcare, USA) at 25°C. uPAR was immobilized on a NiHC 1500M chip (Xantec, Germany) and the interaction was measured at 2.5, 5, 10, 20, and 40 nM with four separate single-cycle kinetic experiments.

**Cell-based assays**

Quantitative flow cytometry using Qifi-kit (Agilent Technologies, USA) was performed according to suppliers instructions. Confluent chamber slides were incubated with primary antibodies, stained with FITC-labelled secondary antibodies and DAPI, and imaged with a DM500 B microscope (Leica Microsystems, Germany). Binding of serially diluted fluorescence antibodies to cell-based plate assays were determined using the Odyssey CLx Imaging System (LI-COR Biosciences, USA). For detailed descriptions of these assays see the Appendix D.

**Animal Models**

The Dutch Central Commission for Animal Experimentation approved all animal experiments (AVD1160020172925). Experiments were performed in accordance with the code of practice ‘Dierproeven In Het Kankeronderzoek”. Each experimental group consisted of three-to-four 6 - 10-week-old female BALB/c-Nude mice (CAnN. Cg-Foxn1nu/Crl, Charles River laboratories, France). Subcutaneous tumor models were induced by subcutaneous injection of 0.5 x 10⁶ UM-UC-3luc2 cells (Appendix D). For the preclinical orthotopic xenograft model, luciferase-expressing UM-U3-luc2 cells were inoculated into the bladder as previously described [18].
In vivo NIRF imaging
Anesthetized (1.5 – 4% isoflurane; Teva Pharmachemie BV, The Netherlands) mice were imaged with The Pearl Trilogy Small Animal Imaging System (LI-COR Biosciences, USA) and Artemis (Quest Medical Imaging, The Netherlands) 1 – 7 days after intravenous tracer injection. After sacrifice, tumors were resected, stained and scanned for 800 nm fluorescence using the Odyssey CLx Imaging System (LI-COR Biosciences, USA).

Photoacoustic imaging
Anesthetized mice were immobilized on the preheated imaging table of the Vevo 3100 Imaging System (FUJIFILM VisualSonics, Canada) and covered with ultrasound gel. The Vevo 3100 Imaging System was equipped with a Vevo LAZR-X cart, a Vevo LAZRTight Enclosure, and a Vevo Imaging Station. For ultrasound and PA imaging, the MX550D transducer (25-55 MHz; Axial Resolution: 40 μm; excitation 780 nm) was used.

Image analyses and statistics
Tumor-to-background ratios (TBRs) were measured by drawing regions of interest around the tumor and the surrounding tissue, and dividing the mean fluorescence intensities (MFIs). In the orthotopic model, either fat or the cecum were used as background to determine tumor-to-organ ratios (TOR). For respective software see Appendix D. Means, reported with standard deviations, were compared by two-way repeated measurement ANOVA with GraphPad Prism 8 (GraphPad Software, USA). Correlations are calculated according to Pearson and indicated by \( R^2 \). Significance levels are \( < 0.05 \).

Results
EpCAM and uPAR are complementary targets for UCC
The IHC expression profiles of EpCAM and uPAR in UCC specimens were compared, as shown in Figure 1A. Staining for EpCAM, when present, was homogenous throughout the tumor, resulting in a moderate to intense membrane staining of malignant cells. However, one-third of cases had no EpCAM expression. uPAR staining was most prominent at the tumor-stroma interface localizing towards cancer cells and tumor-associated stromal cells, including macrophages (CD68 positive) and cancer associated fibroblasts (αSMA positive) (Figure 1B). Staining was moderate to strong in intensity at the cell membranes. Approximately two-thirds of tumor over-expressed uPAR. EpCAM expression did not correlate with either epithelial uPAR
Molecular imaging of uPAR in urothelial cell carcinoma

(R² = 0.20, p = 0.30) or stromal uPAR (R² = 0.21, p = 0.30), see also Appendix E. All in all, 79% of patients overexpressed one or both targets. Expression patterns matched those seen in literature (Appendix F). In addition, mRNA expression levels of PLAUR and EpCAM on UCC tumor cells was independent of each other and confirmed their complementary nature (p = 0.0059, Appendix G).

Figure 1. UCC expression of uPAR and EpCAM. (A) Consecutive sections of a UCC case showing absent to weak EpCAM immunohistochemistry staining at the tumor borders and intense staining for uPAR in both tumor cells and tumor-associated stroma. (B) uPAR positive stroma cells are, amongst others, CD68 positive macrophages and αSMA positive cancer-associated fibroblasts. Black line = 1000 µm. Black box = insert. EpCAM, epithelial cell adhesion molecule; HE, hematoxylin & eosin; UCC, urothelial cell carcinoma; uPAR, urokinase plasminogen activator receptor; αSMA, α-smooth muscle actin.

Using a panel of UCC cell lines, spanning the clinical range from NMIBC to MIBC, we assessed the number of copies for uPAR and EpCAM per cell. Six out of seven cell lines expressed uPAR, ranging from 7,000 – 84,000 copies per cell (Table 1). For EpCAM 4/7 cell lines were positive, ranging from 60,000 - 226,000. In summary, each cell line expressed either uPAR, EpCAM or both, with T24 as possibly problematic cell line, depending on only 7,000 uPAR copies and none for EpCAM.

Table 1. Number of uPAR and EpCAM receptors per cell on UCC cell lines.

<table>
<thead>
<tr>
<th>Cell line</th>
<th>uPAR</th>
<th>EpCAM</th>
</tr>
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<tbody>
<tr>
<td>UM-UC-3luc2</td>
<td>20,000</td>
<td>n.d.</td>
</tr>
<tr>
<td>J82</td>
<td>84,000</td>
<td>n.d.</td>
</tr>
<tr>
<td>T24</td>
<td>7,000</td>
<td>n.d.</td>
</tr>
<tr>
<td>RT112</td>
<td>25,000</td>
<td>139,000</td>
</tr>
<tr>
<td>RT4</td>
<td>n.d.</td>
<td>226,000</td>
</tr>
<tr>
<td>HT-1197</td>
<td>17,000</td>
<td>194,000</td>
</tr>
<tr>
<td>HT-1376</td>
<td>7,000</td>
<td>64,000</td>
</tr>
</tbody>
</table>

EpCAM, epithelial cell adhesion molecular; n.d., not detectable, below detection limit; UCC, urothelial cell carcinoma; uPAR, urokinase plasminogen activator receptor.
**MNPR-101 targets domain 2-3 of uPAR with nanomolar affinities**

Ideally, tracers for molecular imaging have a high affinity for all tumor-associated isoforms of the target. Humanization of ATN658 into MNPR-101 did not alter the affinity for recombinant uPAR with a $K_D$ for ATN658 of $0.5 \times 10^{-9} \text{ M}$ ($K_a 1.6 \times 10^5 \text{ M}^{-1} \text{ s}^1$; $K_d 7.0 \times 10^{-5} \text{ s}^{-1}$) and MNPR-101 having a $K_D$ of $0.2 \times 10^{-9} \text{ M}$ ($K_a 3.6 \times 10^5 \text{ M}^{-1} \text{ s}^1$; $K_d 7.8 \times 10^{-5} \text{ s}^{-1}$). MNPR-101 binding was specific for the cell membranes of uPAR WT and D2-3 HEK cells but not HEK EV cells (Figure 2A-B).

**Figure 2.** In vitro validation of MNPR-101. (A) MNPR-101 binding per flow cytometry to EV, WT and cleaved D2-3 transfected HEK cell lines. (B) Upon immunofluorescence microscopy binding could be seen to localize towards the cell membranes of WT and cleaved D2-3 transfected HEK cells but not EV transfected HEK cells. Green is MNPR-101 signal and grey/blue is a nuclear staining. Bar = 50 µm. (C) After conjugation to a near-infrared fluorescence dye, MNPR-101-800F demonstrated a concentration-dependent 800 nm signal increase on uPAR transfected HEK cells as measured using the Odyssey CLx. Au, arbitrary unit; Conj, conjugate; D2-3, domain 2-3; EV, empty vector; HEK, human embryonic kidney; MFI, mean fluorescence intensity; uPAR, urokinase plasminogen activator receptor; WT, wildtype.

MNPR-101 was conjugated with 800F at a 1.1-1.5 labelling-ratio, and was checked for unconjugated dye, as confirmed by respectively MALDI-TOF analysis and SDS-PAGE scanning. Conjugation did not substantially affect the affinity of MNPR-101-800F for uPAR ($K_D 0.3 \times 10^{-9} \text{ M}$; $K_a 6.1 \times 10^5 \text{ M}^{-1} \text{ s}^1$; $K_d 1.5 \times 10^{-5} \text{ s}^{-1}$). A dose-dependent increase of 800 nm signal on cell-based plated assays with HEK uPAR WT and uPAR D2-3 cells, and constant low signal with HEK EV cells confirmed binding capacity (Figure 2C).

**NIR Image-guided surgery of UCC with MNPR-101-800F**

Fluorescence tracers can accumulate in tumors due to nonspecific effects such as the enhanced-permeability and retention effect or blood pooling. In order to account for this effect, two non-cancer related humanized monoclonal antibodies were
used as non-specific controls. In vitro, MNPR-101 but not Infliximab (anti-TNFα) or Rituximab (anti-CD20) bound UM-UC-3luc2 cells (Figure 3A).

Figure 3. NIR fluorescence imaging with MNPR-101-800F. (A) Flow cytometry of MNPR-101, Infliximab and Rituximab of UCC UM-UC-3luc2 cells. (B) In vivo tumor MFIs determined using the Pearl imaging system and (C) TBRs determined by the Artemis imaging system after intravenous injection of 0.33, 1 and 3 nmol MNPR-101-800F in subcutaneous UM-UC-3luc2 tumor-bearing mice. (D) In vivo TBRs determined by the Artemis imaging system after intravenous injection of 1 nmol MNPR-101-800F, Infliximab-800F or Rituximab-800F. (E) NIR-images of subcutaneous UM-UC-3luc2-bearing mice four days after administration of MNPR-101-800F, Infliximab-800F and Rituximab-800F. NIR images were taken with the clinical Artemis NIR-camera. A representative tumor (T) and background (B) ROI is shown. Au, arbitrary unit; Conj, conjugate; d, day; h, hour; MFI, mean fluorescence intensity; NIR, near-infrared; nmol, nanomole; TBR, tumor-to-background ratio.

The in vivo tumor recognition potential was subsequently assessed in mice bearing UM-UC-3luc2 subcutaneous tumors. Total mouse tumor burden did not differ significantly between experimental groups ($p = 0.6581$). After intravenous injection of 0.33 nmol, 1 nmol and 3 nmol MNPR-101-800F, mice were imaged daily with the preclinical Pearl and clinical Artemis imaging systems. Tumor MFI corresponded
with the injected dose \((p < 0.0001, \text{Figure 3B})\). TBRs did not differ significantly between dose groups with sufficient TBRs 3-7 days after imaging (Figure 3C) and a TBR max of 2.9 five days after injection of 1 nmol MNPR-101-800F.

As specificity controls, subcutaneous UM-UC-3luc2-bearing mice were injected intravenously with 1 nmol Infliximab-800F or Rituximab-800F. TBRs differed significantly between MNPR-101-800F and the controls across all time points except for 4 hours post injection \((p < 0.0001, \text{Figure 3D})\). In contrast to Infliximab-800F or Rituximab-800F, tumors were readily visualized with the clinical Artemis system starting 3 days after MNPR-101-800F injection (Figure 3D-E).

Intravesical injection of bioluminescent UM-UC-3luc2 cells into the murine bladder represents a preclinical orthotopic UCC model that allows optical imaging of cancer growth in real time [18]. Three weeks post tumor inoculation 1 nmol MNPR-101-800F and Rituximab-800F were injected intravenously and imaged three days later. Tumors where highly fluorescent after MNPR-101-800F injection matching bioluminescence signal and allowing image-guided resection (Figure 4A, Appendix H). Importantly, post-mortem histology, fluorescence scanning and immunohistochemistry confirmed tumor cell specificity of MNPR-101-800F and only non-specific signal with Rituximab-800F (Figure 4B). MNPR-101-800F exhibited an average tumor-to-fat ratio of 2.6 (range: 2.3 – 3.2) and tumor-to-caecum ratios of 5.8 (range: 5.3 – 6.8) (Figure 4C). The tumor-to-fat ratio and tumor-to-caecum ratio for Rituximab-800F were 1.3 and 3.2, respectively. On post-mortem biodistribution analysis of MNPR-101-800F, the majority of the fluorescence was seen in the tumor followed by the metabolizing organs (Figure 4D). The CD20 targeting Rituximab-800F preferentially localized towards the liver and kidneys.

**Photoacoustic imaging of UCC with MNPR-101-800F**

The multi-modal imaging potential of MNPR-101-800F was investigated by PA-imaging. Subcutaneous UM-UC-3luc2 tumor-bearing mice were injected intravenously with 3 nmol MNPR-101-800F and imaged three days post-injection. High intensity signal was evident throughout the tumor and the skin while signal in surrounding structures remained minimal (Figure 5A). Nonspecific signal was noticed in the skin of PBS-injected negative control mice (Figure 5B).
Figure 4. uPAR NIR-guided surgery in a preclinical orthotopic UCC xenograft model. (A) Bioluminescence imaging and NIR image-guided resection with the clinical Artemis NIR camera three days after 1 nmol injection of MNPR-101-800F or Rituximab-800F. (B) Post-mortem histological, fluorescence scanning (Odyssey) and uPAR immunolocalization of resected orthotopic tumors (C) In vivo signal-to-background ratios measured during image-guided resection with the clinical Artemis NIR camera and (D) post-mortem whole-body biodistribution determined using the Pearl. Ce, cecum; F, fat; HE, hematoxylin & eosin, NIR, near-infrared; nmol, nanomole; TOR, tumor-to-organ ratio; UCC, urothelial cell carcinoma; uPAR, urokinase plasminogen activator receptor.
Discussion

The recurring nature of UCCs and the tendency to progress are a significant burden for patients and health services [19, 20]. Consequently, every effort should be made to improve therapy. Here we implemented a novel approach that may facilitate and improve UCC detection and resection rates by intraoperative multi-modal guidance utilizing MNPR-101-800F.

The additional value of exogenous contrast agents during cystoscopy has already been demonstrated with 5-aminolevulinic acid (5-ALA) and its fluorescence metabolite protoporphyrin IX (PpIX) [21]. Using 5-ALA, 7-30% more UCCs were detected, residual tumor rate reduced by 20% and cancer-free survival increased. However, the fluorescence properties of PpIX (excitation 375-440 nm, emission 635, 704 nm) are poor regarding penetration depth, tissue absorption and scattering, and tissue autofluorescence and not adapted to most clinically used NIR imaging systems [22]. The favorable imaging characteristics of NIR-fluorophores pave the way for improved real-time NIR fluorescence guided resection of UCC.

To date, no single tracer is suitable for intraoperative guidance of all UCC specimens. As a result, a tracer library should be developed from which a surgeon can select the most suitable tracer [8]. Ideally, these tracers visualize unique characteristics of UCC which distinguishes the tumor from adjacent normal tissue. In case of uPAR and EpCAM, these membrane receptors have complementary expression patterns during the complex multistep process of switching from a sessile to an invasive cancer cell [23, 24]. In addition to uPAR targeting, we show our recently introduced EpCAM-targeting tracer, which is currently being evaluated on patients with gastrointestinal cancer, could also be used for UCC (NL7363) [25]. Other potential combinations encompass EGFR, HER2 and/or matrix-metalloproteases, some of which are currently being investigated in clinical studies with other tumor
types [8]. Release of these membrane proteins into the urine provide a possible surrogate biomarker for their respective tumor expression and provides a simple non-invasive method for tracer selection. While both uPAR and EpCAM are elevated in urine from UCC patients, the correlation with cellular expression has not yet been evaluated [26-29].

Although NIR-imaging has superior resolution, it is less suitable for imaging of lesions deeper than 1 cm [8]. PA, on the other hand, provides molecular contrast of up to 12 cm deep without compromising on the submillimeter spatial resolution. As a result, PA has been utilized for in vivo imaging of organelles to organs, and has been incorporated in imaging platforms for transvaginal imaging of ovarian cancer and transrectal imaging of prostate cancer [30-32]. In the case of UCC, improved imaging depth allows the visualization of deeper layers of the bladder, including the muscularis propria and per-vesical fat, informing urologists of possible advanced T-stage disease during cystoscopy and the need of the more aggressive (partial) cystectomy [33, 34].

We investigated whether NIR fluorescence-imaging could be performed in combination with PA, by utilizing a contrast agent with a reasonable extinction coefficient and relatively low quantum yield (for PA-imaging a large non-fluorescence relaxation is desired), such as 800F ($\varepsilon = 2.4\times10^5$; $\Phi = 0.034$) [14]. In a proof-of-principle study, Tummers et al. imaged pancreatic cancer ex vivo using both fluorescence and PA-imaging modalities [35]. Similarly, the development of liver metastases in vivo was monitored bimodally using a single $\alpha_v\beta_3$ integrin targeting contrast agent, Angiostamp800 [36]. Our results show the feasibility of imaging through superficial structures such as the skin.

uPAR bimodal imaging is not limited to MNPR-101-800F. Its precursor, ATN-658 was previously dual labelled for SPECT and NIR imaging using the hybrid $^{111}$In and ZW800-1 label for imaging of locoregional oral and colorectal cancer. While procuring TBRs of $5.0 \pm 1.3$ and being able to visualize 1-2 millimeter sized lesions, the tracer is less suitable for PA imaging due to ZW800-1 quantum yield ($\varepsilon = 2.5\times10^5$; $\Phi = 0.150$) [12, 13, 37]. Another option is the uPAR targeting peptide AE105-Glu-Glu-ICG which has successfully identified multiple tumor types in various preclinical models with TBRs up to $3.5 \pm 0.2$ [38, 39]. Its fluorophore, indocyanine green (ICG) has a similar extinction coefficient and quantum yield as 800F ($\varepsilon = 2.7\times10^5$; $\Phi = 0.027$) and has been used for previously for PA imaging [14]. Peptides generally clear rapidly from the circulation via the kidneys, which could be a limiting factor for bimodal imaging of UCC [40].
Conclusion

uPAR and EpCAM are complementary targets for NIR imaging of UCC that are indicative of separate tumor differentiation states. MNPR-101-800F targets uPAR and allows for simultaneous NIR and PA guidance. If confirmed in a clinical setting, such assistance can result in a paradigm shift, altering how urologists survey and treat UCC, thus potentially improving patient outcomes.
References


