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Editorial

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Targeting Prostatic Acid Phosphatase in Prostate Cancer: Roadmap on How To Venture Above and Beyond Prostate-specific Membrane Antigen with ACP3 Theranostics

Cristiano Pini[a], *Fabrizia Gelardi*[b], *Martina Sollini*[a,b], *Arturo Chiti*[a,b,*]

[a] *Vita-Salute San Raffaele University, Milan, Italy;* [b] *Department of Nuclear Medicine, IRCCS San Raffaele Hospital, Milan, Italy*

Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) has become the reference imaging modality across the natural history of prostate cancer (PC) [1], while PSMA-targeted radioligand therapy (RLT) is now an established treatment option in the post-taxane castration-resistant setting, with encouraging data in earlier disease phases also emerging. Despite this success, PSMA is not without limitations. Nonspecific bone uptake can complicate image interpretation and [2] requires careful clinical interpretation. Moreover, heterogeneous or low PSMA expression may impair diagnostic accuracy and exclude a relevant proportion of patients from PSMA-based RLT [3,4]. Finally, particularly in the setting of α-particle–emitting therapies, salivary gland uptake remains a clinically meaningful drawback that often translates to significant xerostomia [5].

Against this background, this issue of *European Urology* includes a report by Backhaus and colleagues [6] on the first-in-human study of prostatic acid phosphatase (ACP3) as a novel and intriguing target for PC theranostics. In their exploratory cohort of 25 patients imaged with [^{68}Ga]Ga-OncoACP3 PET, the authors observed a favourable biodistribution profile, characterised by negligible salivary gland uptake and high tumour-to-background ratios. Notably, in almost half of the patients, ACP3 PET outperformed [^{18}F]PSMA-1007 PET for lesion detection, which suggests that ACP3 may capture a biologically relevant disease signal that is at least partly complementary to PSMA.

These findings naturally prompt several clinically relevant questions. The performance of ACP3 PET across different disease settings deserves careful investigation. At initial diagnosis and during local staging, higher ACP3 expression in benign prostate tissue and low-grade disease could potentially increase sensitivity at the expense of specificity. Conversely, in heavily pretreated patients and those with advanced PC—such as those included in the study by Backhaus et al—PSMA PET appears to retain a slight advantage. An understanding of at which point along the disease continuum ACP3 adds the greatest incremental value will be essential to avoid indiscriminate use and to guide rational clinical adoption.

Beyond imaging, ACP3 holds particular promise as a theranostic target. The lack of salivary gland uptake raises the prospect of a more favourable safety profile for RLT, and ACP3 could potentially mitigate one of the most relevant dose-limiting toxicities observed with PSMA-based approaches. However, promise alone is insufficient. The development of ACP3 theranostics should be guided by a clear strategy aimed at generating robust, clinically meaningful evidence and facilitating an efficient regulatory pathway.

The PSMA experience offers valuable lessons in this regard. Practice-changing imaging was achieved not via an accumulation of retrospective studies, but through well-designed prospective trials addressing concrete clinical questions and focusing on patient-level impacts. Translation of this paradigm to ACP3 means starting from unmet clinical needs rather than from the tracer itself, adopting robust reference standards, and prioritising endpoints that reflect changes in management and patient outcomes rather than lesion counts alone. Similarly, ACP3-targeted

* Corresponding author. Department of Nuclear Medicine, IRCCS San Raffaele Hospital, Milan, Italy.
E-mail address: chiti.arturo@hsr.it (A. Chiti).

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RLT should be evaluated in comparative trials using appropriate standard-of-care comparators and clinically relevant endpoints that should include survival, symptom control, and patient-reported outcomes. Clear biological and imaging criteria for defining ACP3 positivity will be critical, as will rigorous and transparent assessments of safety.

Equally important is the adoption of a multidisciplinary approach. The success of PSMA theranostics has been driven in part by close collaboration between nuclear medicine physicians, urologists, oncologists, and radiation oncologists. Further strengthening such collaboration for ACP3 will be crucial to ensure that innovation remains anchored to real-world clinical decision-making and patient benefits.

At the same time, several pitfalls should be actively avoided. The rapid proliferation of retrospective and methodologically heterogeneous studies risks the generation of noise rather than knowledge, as recently observed for many emerging radiopharmaceuticals. Similarly, framing the development of ACP3 primarily as a competitor to PSMA would be reductive and potentially misleading. The relevant question is not which tracer is "better" in absolute terms, but which tool, applied to which patient population, and in which disease stage leads to better decisions and outcomes [7,8]. Finally, small, underpowered studies focusing solely on diagnostic accuracy are unlikely to support widespread clinical adoption in an era in which imaging increasingly drives treatment escalation or de-escalation; therefore, we should prioritise studies that can truly serve this purpose.

ACP3 theranostics may indeed represent the next significant step forward in PC management, whether as an alternative or complement to PSMA-based approaches. The opportunity is substantial, but so is the responsibility. By building on successes from the PSMA era and avoiding the most common missteps, the field has a chance to move from compelling images to durable clinical value that may ultimately benefit the patients who this innovation is intended to serve.

Conflicts of interest: Cristiano Pini, Martina Sollini, Fabrizia Gelardi, and Arturo Chiti are investigators in a phase 1 clinical trial of [^{68}Ga]Ga-OncoACP3 (NCT06840535) sponsored by Philogen S.p.A. Arturo Chiti reports consulting or advisory roles for Blue Earth Diagnostics, Telix Pharmaceuticals, InnovaRadi Therapeutic, and General Electric Healthcare; speaker honoraria from Bracco Diagnostics, General Electric Healthcare, Novartis, Telix Pharmaceuticals, and United Imaging Healthcare; and an Editor in Chief role for the *EANM Journal*. Martina Sollini reports speaker honoraria from Elma Academy, Train SRL, Accademia Nazionale di Medicina, and General Electric Healthcare; and an Associate Editor role for *Cancer Imaging*.

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