$^{212}$Pb-DLL3 Radio-DARPin shows promising Preclinical Antitumor Efficacy in Small Cell Lung Cancer

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• All authors are employees of Molecular Partners and Orano Med
• Christian Lizak has ownership of stocks in Molecular Partners
DARPin Therapeutics: Opportunity in Nuclear Oncology?

**DARPins in Oncology & Beyond**

- Close the gap between small molecules & antibodies
- Broad target range, binders against >60 targets
- 7 clinical-stage compounds, >2500 patients treated

**The Challenge for Radiotherapeutic Applications**

**Imaging of Breast Cancer**

**1st BioD in Tumor Mouse Model**

Unlocking DARPin for Radiotherapeutic Applications

1) Increase Tumor Uptake
2) Reduce Kidney Accumulation

Adopted from Bragina et al., J Nuc Med, 2021
Radio-DARPin Platform Ready to Deliver Product Candidates

Increased Tumor Uptake by half-life extension (HLE)*

Reduced Kidney Accumulation by surface engineering (Stealth DARPin)*

Optimized Biodistribution Properties

Intrinsic DARPin Properties

✓ Small Size (~15 kDa)
  → Deep tumor penetration
  → Short systemic half-life

✓ High Affinity (pM range)
  → Long tumor retention

✓ High Selectivity
  → Low accumulation in other tissues

✓ High Stability
  → Surface Engineering

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* Data presented at various scientific conferences, including AACR 2023 (Bosshart et al.), SNMMI 2023 (Lizak et al.), EANM 2023 (Lizak et al.), and others
The first $^{212}$Pb-DLL3 Targeted Radiotherapy

Combining distinctive DARPin features with the power of $^{212}$Pb for efficacious cancer therapy

**SCLC as Indication**
- Aggressive cancer with high unmet medical need
  - 2L: mPFS ~3m; 5y OS ~3%\(^1,2\)
  - DLL3 is expressed in >85% of pts\(^3\)

**DLL3: A promising Target**
- Homogeneous tumor expression, but low expression level in pts
- No expression in healthy tissues
- New treatments with room for improvement: Tarlatamab (AMGEN) for 2L+; ORR ~40%

**Diverse set of DARPinns against DLL3**
- Good developability
- Specific binding with high affinity

**PRODUCT COMPOSITION**

- Tunable albumin binding

**212Pb for Targeted Alpha Therapy**
- Strong cytotoxicity (dsDNA breaks)
- Single alpha decay (limited free daughters)
  - Limited irradiation of healthy tissues
- Relatively short half-life (10.6 h)
  - Fast energy deposition (efficacy)
  - Easier waste management

**Co-Development with Orano Med**
- The leader for $^{212}$Pb & a committed partner
- Reliable & scalable $^{212}$Pb production
- Independent production capacities (substantial inventory of purified $^{232}$Th)

**ASCO: Ph2 clinical data $^{212}$Pb-DOTAMTATE (AlphaMedix\(^\text{TM}\)) showed an ORR of 55.6%\(^4\)**

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1) Treatment of refractory and relapsed small cell lung cancer, UpToDate
2) SEER
3) Rojo et al., Lung Cancer, 2020
4) Strosberg et al., ASCO 2024 presentation
Promising Biodistribution Profile of $^{212}$Pb-DLL3 RDT Candidate

- Positive tumor to non-tumor ratio
  - Tumor to kidney ratio of 1.4:1 (AUC)
- Strong and homogenous tumor uptake confirmed by alpha camera
- Elevated blood levels (caused by half-life tuning) are quickly decreasing

**MC38-hDLL3 Model with Elevated DLL3 Expression Level**

<table>
<thead>
<tr>
<th>Time Point</th>
<th>T : K</th>
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<tbody>
<tr>
<td>4 h</td>
<td>1.4 : 1</td>
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<tr>
<td>24 h</td>
<td>1.5 : 1</td>
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<tr>
<td>AUC (&lt; 24 h)</td>
<td>1.4 : 1</td>
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</tbody>
</table>

Mice xenografted s.c. with hDLL3-MC38 (Biocytogen)
Dose: 10 μCi of $^{212}$Pb at 0.01 mg/kg of DLL3 DARPin

*other healthy organs with levels ≤ 5%ID/g not shown*
Favorable Safety & Potent Efficacy of $^{212}$Pb-DLL3 RDT Candidate

**Dose Range Finding in wt Mice**

- All treatments up to 40 µCi were well tolerated
  - Treatment shows a favorable safety profile suggesting its potential for clinical use

**Efficacy in MC38-hDLL3 Model**

- Significant and durable inhibition of tumor growth (comparable to benchmark mAB)
  - Treatment shows profound antitumor activity at clinically relevant dose

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Mice xenografted s.c. with hDLL3-MC38 (Biocytogen)
Dose: 10 µCi of $^{212}$Pb at 0.01 mg/kg of DLL3 DARPin
MP0712: $^{212}$Pb-DLL3 Lead Candidate with Attractive BioD Profile

- **MP0712 Lead Candidate** shows encouraging BioD profile with **T:K Ratio >2** in MC38 model
- Similar profile in NCI-H82 model (patient relevant DLL3 expression) with T:K Ratio >1 (data not shown)
Summary – Radio-DARPin Therapy (RDT)

✓ Successful RDT platform optimization for reduced kidney accumulation and increased tumor uptake
✓ **MP0712 selected as Lead Candidate for $^{212}$Pb-DLL3 targeted Radio-DARPin Therapy**
✓ IND-enabling activities initiated with Orano Med; FIH clinical data expected in 2025

**Outlook:**
- Advance **MP0712** and additional pipeline candidates
- Evolve RDT platform
- Progress collaboration projects with Orano Med and Novartis

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<th>TARGET</th>
<th>RESEARCH</th>
<th>DEV.</th>
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<tbody>
<tr>
<td>DLL3</td>
<td>MP0712</td>
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<td>Target 2*</td>
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<td>Target A</td>
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<td>Target Y</td>
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<td>Several targets in evaluation</td>
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* The co-development agreement with Orano Med includes up to 3 potential oncology targets including DLL3 (Delta-like ligand 3)
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