WARF THERAPEUTICS
Invest-Develop-Partner

# Radiopharmaceutical for CA9+ cancers


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# Our goal: develop a best-in-class radiopharmaceutical for CA9+ cancers

- **WARF Therapeutics** is developing a radiopharmaceutical for the treatment of CA9+ cancers
- Our molecules are highly potent and selective with **superior off-rates**
- This resulted in **greater tumor uptake, and longer tumor retention times** compared other CA9+ radiotherapeutics under development
- This led to **higher doses delivered to the tumor** driving **superior efficacy**
- Interim animal efficacy results confirm our hypothesis
- We are seeking a partner that can continue the development and commercialize this radiopharmaceutical so that we can help the patients that need it the most

# Partnering opportunity for CA9 targeting radiopharmaceutical

## Program WT-735

- **Target:** Carbonic Anhydrase 9 (CA9)
- **Primary indications:** non small cell lung cancer and metastatic clear cell renal cell carcinoma
  - Secondary indications include prostate, bladder, breast, ovarian, pancreatic, and head and neck cancers
- **Modality:** Small molecule radiolabeled with a beta-emitter (Lu-177)
- **Development stage:** Lead optimization
- **Progress to date**
  - Therapeutic and imaging lead candidates identified
  - In vitro and in vivo PoC in ccRCC mouse models
  - Interim efficacy data in mouse model
  - Efficacy study to be complete in July

# There is a large unmet need in CA9+ NSCLC and metastatic ccRCC

| | 5-year relative survival | United States Incidence for CA9+ | Worldwide Incidence for CA9+ | Worldwide Market 2023 |
|---|---|---|---|---|
| NSCLC | 28% | 54,636 | 411,400 | $31.5B |
| Metastatic ccRCC | 18% | 11,398 | 47,769 | $10.1B |

Additional indications include prostate, bladder, breast, ovarian, pancreatic, and head and neck cancers

[1] EvaluatePharma
[2] Medicine (2019) 98:31(e16684)
[3] JCO Oncology Practice, Volume 18, Number 3
Worldwide includes North America, EU, China, Japan and S. Korea

# Radiopharmaceuticals are the future for metastatic ccRCC therapy

## Radiopharmaceuticals Programs in Development for ccRCC

| Company | Name | Compound | Stage | Mechanism of Action | Indication |
|---|---|---|---|---|---|
| **Telix** | TLX250 | $^{177}$Lu-girentuximab | Phase II (STARLITE 1 & 2) | Immune system "primer" in combo with Cabometyx + Opdivo for 1st line and with Opdivo for 2nd line treatment | ccRCC (1st line and 2nd line) |
| **Telix / ATONCO** | α-TLX250 | $^{211}$At-girentuximab | Preclinical | Alpha radiation emitter (astatine-211) | Bladder cancer (potential for ccRCC) |
| **RayzeBio** | RAYZ-15710 | Small molecule with radiation emitter | Preclinical | Radiation emitter | ccRCC |
| **DebioPharm** | Debio 0228 | Peptide with Lu | Phase II | Radiation emitter | Metastatic ccRCC |
| **WARF Therapeutics** | WT 735-0626<br>WT 735-0729 | Small molecule with radiation emitter | Preclinical | Radiation emitter | ccRCC |

# WT candidates are highly potent and selective for CA9

## *Biophysical Profile:*

| SPR KD (nM) / $t_{1/2}$ (min) | WT-735-0626 | WT-735-0729 |
|---|---|---|
| **CA9** | **0.03 / 490** | **0.05 / 220** |
| CA4 | 11 / 10 | 6 / 13 |
| CA12 | 9 / 31 | 3 / 34 |
| CA14 | 4 / 15 | 2 /22 |

## *Cell Membrane Binding (nM):*

| | | |
|---|---|---|
| CA9 (nM) (CaSki) | 0.8 | 0.4 |
| CA12 (nM) (A498) | 32 | 19 |
| SK-RC-52 (nM) | 0.2 | 3 |

## *Solubility and in vitro DMPK:*

| | | |
|---|---|---|
| Solubility (µM) | 300 | 260 |
| logD | -1.1 | -2.1 |
| Mouse PPB (%) | 77 | 70 |
| Mouse microsomal CL (ml/min/kg) | 0 | 0 |

## *Mouse PK*

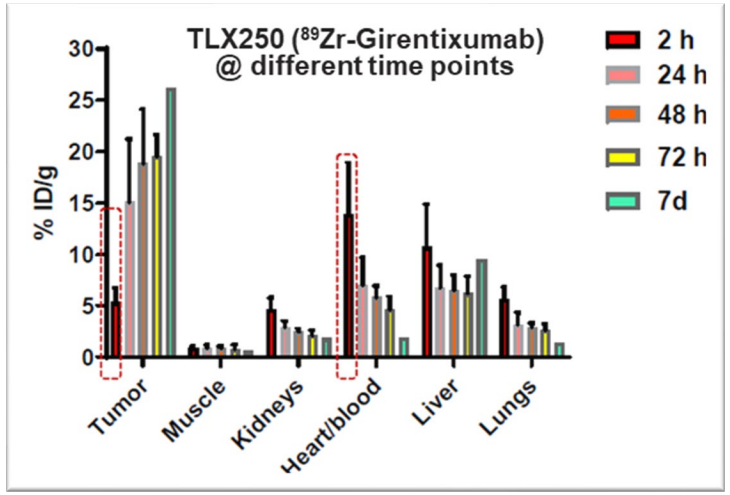
| PK parameters | Unit | 0626 Mean | 0729 Mean |
|---|---|---|---|
| Cl_obs | mL/min/kg | 8.42 | 22 |
| $T_{1/2}$ | h | 1.45 | 2.10 |
| $C_0$ | umol/L | 4.71 | 3.00 |
| $AUC_{Inf}$ | h*umol/L | 1.90 | 1.90 |
| $V_{ss}$_obs | L/kg | 0.315 | 0.65 |

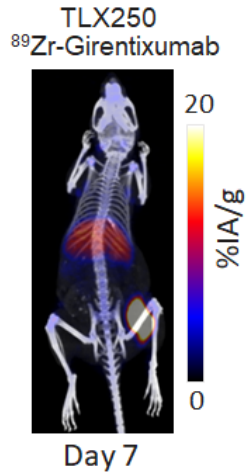
## WT candidates demonstrated

- **Excellent CA9 binding affinity** with **long residence times**
- **> 100-fold selectivity** vs. other CAs
- Excellent *in vitro* and *in vivo* mouse PK profile

# WT candidates show greater tumor uptake and faster blood clearance than Telix's TLX250

## Telix

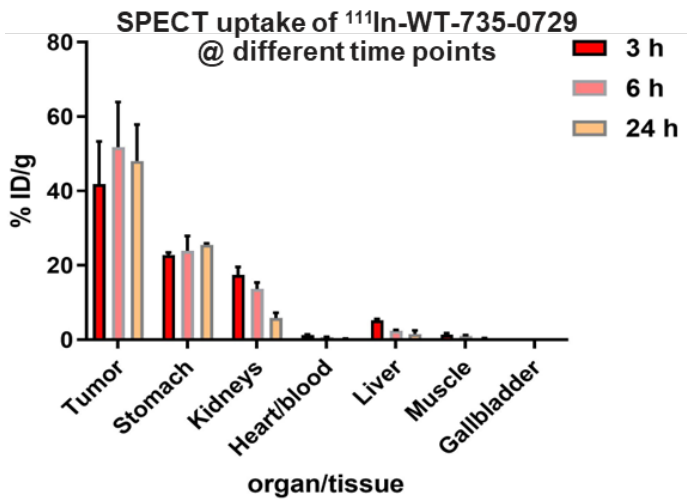


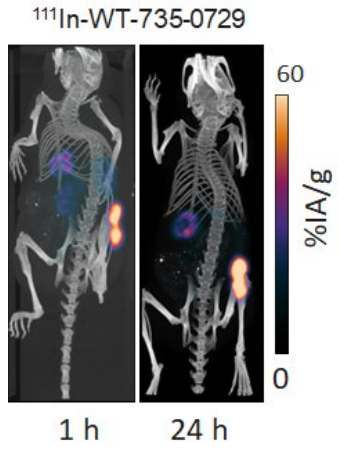



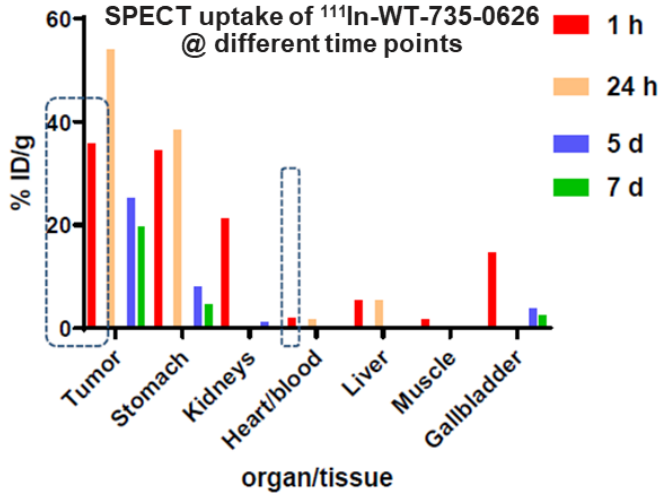

### Telix250 demonstrated

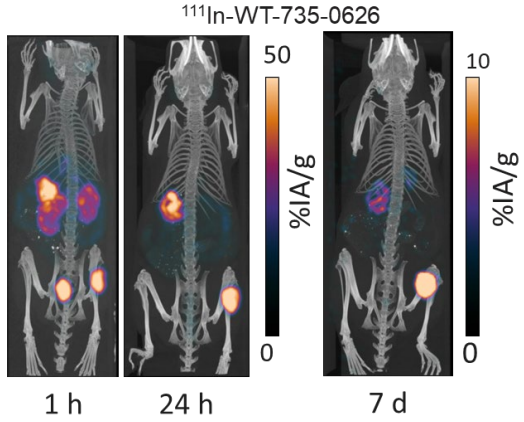
- **Slow tumor uptake** that peeks @ day 7
- Significant concentrations in other organs at previous time points

## WARF Therapeutics




- WT-0626 shows **outstanding tumor uptake (~38% ID/g)** @ 1hr
- WT candidates show between **~3.2x to ~3.5x greater tumor uptake** @24h compared to TLX250
- **Rapid blood clearance** with reduced uptake in liver, lungs and heart compared to TLX250
- Variable/tunable "on-target" uptake in stomach

# WT candidates have best in class potential

## WT vs. RayzeBio and DebioPharm

**WT candidates have comparable selectivity with superior off-rates, greater tumor uptake, longer tumor retention and improved dosimetry (~3 Gy/MBq)**

| Compound | CA9 potency (nM) / off-rate (min) | CA12 selectivity / off-rate (min) | % of dose in tumor | | $^{177}$Lu therapeutic dose (mCi) | Potential Tox |
|---|---|---|---|---|---|---|
| | | | 24 h | 7 d | | |
| WT-735-0626 | 0.03 / 490 | 300 / 31 | **55%** | **18%** | 0.5 | stomach |
| WT-735-0729 | 0.05 / 220 | 120 / 34 | **54%** | Data pending | 0.5 | stomach |
| RAYZ-15710 | 0.09 / 27 | 1500 / NR | 6% | **<3%** | 3.0 | Kidney/stomach |
| DPI-4452 | 0.25 / 99 | NR | **10% (4 h)** | **NR** | 3.0 | Kidney/stomach |

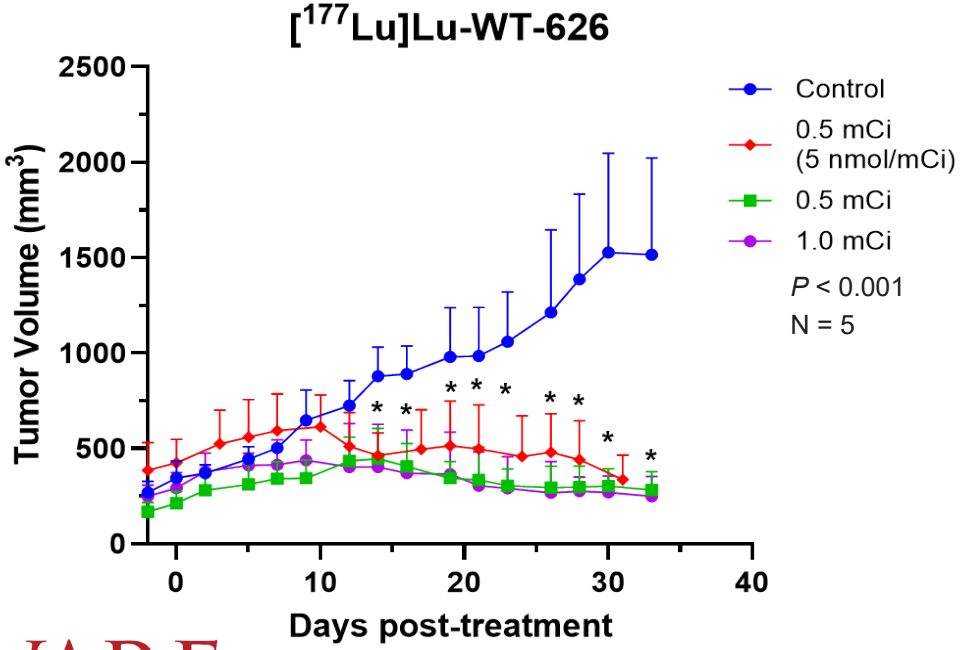
NR: Not reported

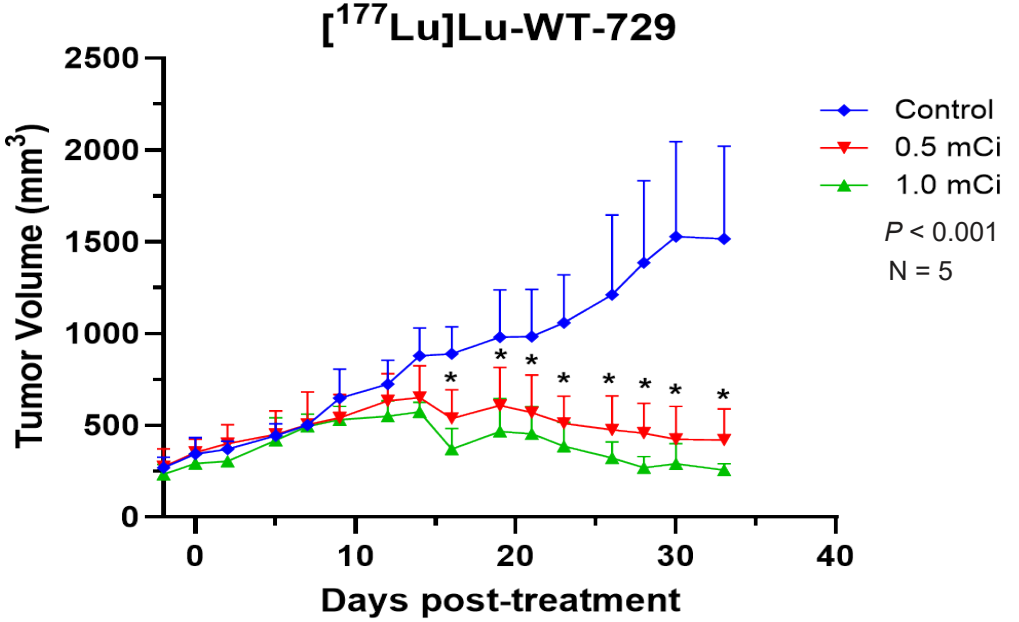
# Animal proof of concept for 626 and 729

- 8 cohorts of 5 mice per cohort
  - 3 conditions for 626, 2 for 729, and 2 for cG250
  - All cohorts will be repeated with 5 additional mice
- Implant tumors in mice on day 1
- Allow tumors to grow for 14 days
- Divide mice into treatment (Lu177) and placebo groups and give a single dose on day 15
- Monitor tumor size, survival (out 120 days), and treatment related toxicity
- WT-735-0626 and 0729 dosed on January 10, 2024

# Efficacy study with WT drugs 626 & 729

- Mice were **dosed with 0.5 to 1.0 mCi** of $^{177}$Lu-WT-626 and $^{177}$Lu-WT-729
- Mice dosed with placebo showed tumor progression of ~350% over 28 days
- Mice treated with either agent showed tumor **regression starting on day 9-12**
- **Statistical significance was achieved at day 12-16** after dosing
- Survival tracking ongoing

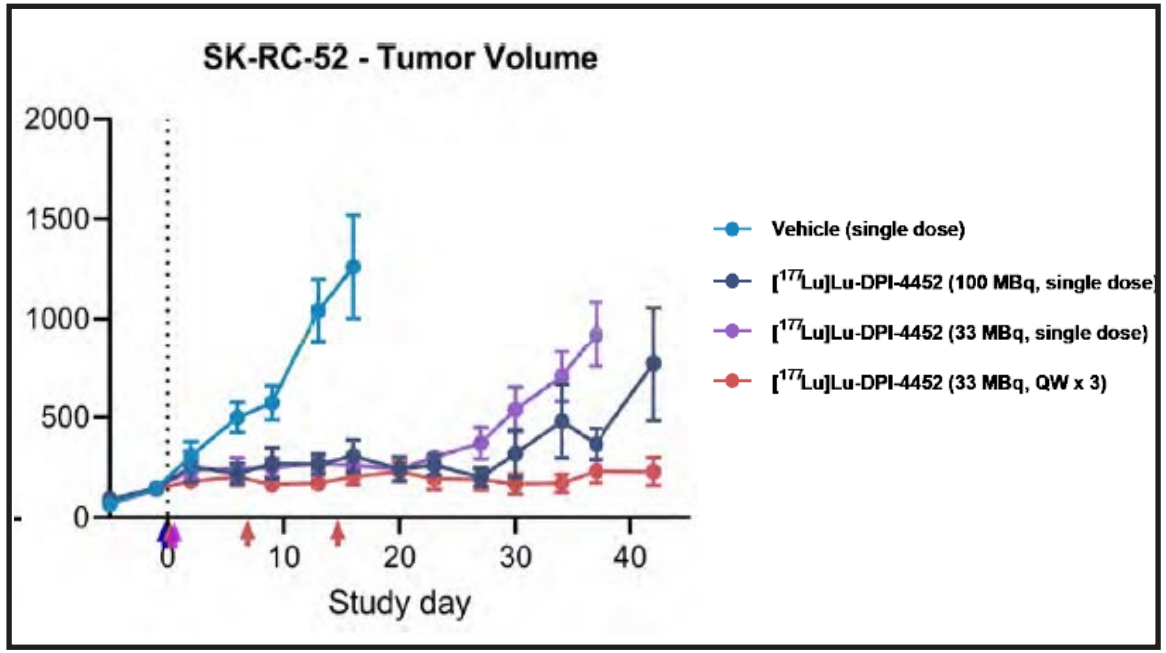


# Efficacy studies for Debiopharm $^{177}$Lu-dpi-4452

## Key results

- Mice receiving placebo (vehicle) grew ~1,500 mm$^3$ after 20 days
- Mice given 3 mCi $^{177}$Lu-DPI-4452 **(6X higher than 626)** achieved only temporary tumor response
- Tumors progressed after day 20 at the same initial growth rate
- To improve response multiple injections of $^{177}$Lu were required

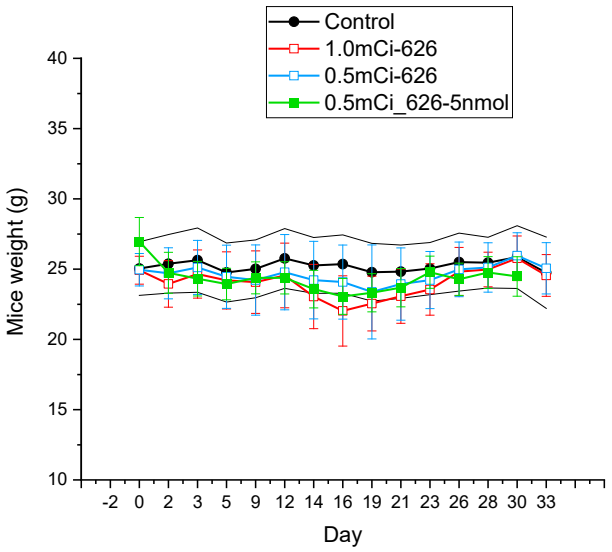


# Mice body weights were unaffected by the treatments

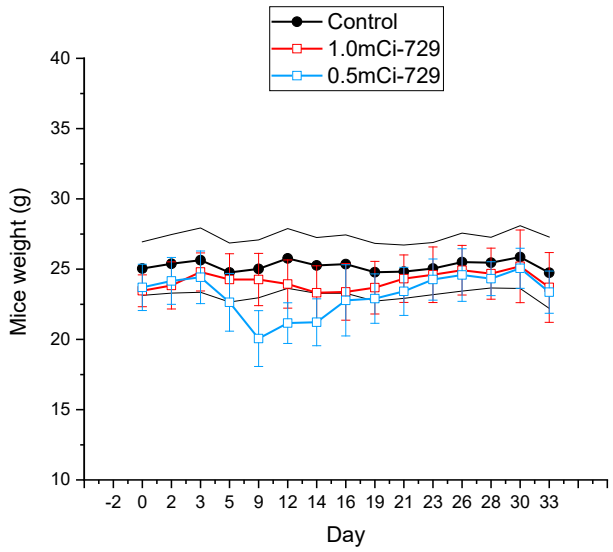
**Dosimetry data estimates that ~90 Gy of radiation can be safely delivered to the tumor without off target effects in the stomach**

**Treatment vs. control**

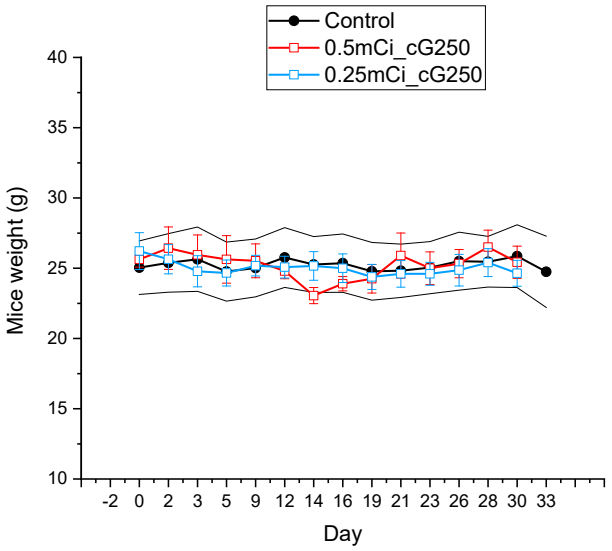
**WARF Therapeutics 626**




**WARF Therapeutics 729**




**Telix cG250**




- *Mouse 3 @ 1.0mCi 626 group excluded from every measurement/dataset (tumor not visible from day 12 to day 26)*
- *Mouse 1 @ 0.5mCi cG250 group excluded from every measurement/dataset (mouse died on 01/29/24 @ day 17)*
- *Group 0.5mCi 729 sick with visible C. Bovis on 01/19/24 @ day 9*

# Next steps

- ccRCC model
  - Dose & schedule optimization
  - Isotope exploration
- Toxicology in normal mice
- Non-human primate biodistribution imaging
- Initiate NSCLC tumor models
- GMP production and IND enabling studies

# CA9 radiopharmaceutical opportunity

**NSCLC and metastatic ccRCC are large indications with high unmet need**

- Upside potential with secondary indications such as bladder, breast, ovarian, prostate, pancreatic, and head and neck cancers

**WT candidates show best in class potential**

- Single dose, mouse efficacy study demonstrates **superior efficacy** compared to RayzeBio's $^{177}$Lu-15170 and DebioPharm's $^{177}$Lu-DPI-4452
- Candidates have comparable selectivity with **superior off-rates, greater tumor uptake, longer tumor retention and improved dosimetry** compared to RayzeBio's $^{177}$Lu-15170 & DebioPharm's $^{177}$Lu-DPI-4452
- Candidates show **greater tumor uptake and faster blood clearance** than Telix's TLX250

**Single dose, efficacy data in mice with Lu-177 will be complete by 2Q 2024**

**WT is seeking a partner to continue the development and commercialize this asset**

- Worldwide, exclusive rights are available
- We are open to various deal structures such as licensing, co-development, build to buy or startup formation

**For more information contact John Nagel at jnagel@warf.org**