

CRT Licensing Opportunity



Novel Radiolabelled Bisphosphonates

- Patented compounds with imaging and therapeutic utility
- Enhanced radiolabel retention and bone selectivity
- Significant potential for increased therapeutic index
- Simple synthesis route and high product stability

SMALL MOLECULES | *In Vivo* Proof-of-Principle

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Commercial Opportunity

Bone metastases are a major problem in many of the largest cancer indications including in breast and prostate cancer. Improved imaging agents or treatments for such patient groups would represent a significant market.

We have developed and patented novel compounds which may overcome the clinical limitations associated with currently used radiolabelled bisphosphonates and increase their utility in these indications.

We are seeking a licensee to undertake further development of these compounds and clinical testing in imaging and/or therapeutic contexts under a licensing or collaborative relationship.

Technology

A wide array of radiolabelled agents are used clinically in imaging and therapeutic applications. One particular class of agents, the bisphosphonates have been used extensively in the treatment of bone disease and radiolabelled versions of these such as ^{99m}Tc -MDP have been developed for the imaging of bone metastases. In addition, beta emitting agents have been developed for palliative use including ^{186}Re -HEDP which has been widely used in the treatment of bone metastases associated pain.

There is also growing evidence that radiolabelled bisphosphonates can be effective in a therapeutic setting with significant effects on survival outcomes reported. For example,

in a phase II trial ^{188}Re -HEDP treatment of bone metastases in late stage prostate cancer patients resulted in a substantial prolongation of overall survival (7 versus 2.3 months) (1).

Despite such promising results, current radiolabelled bisphosphonate agents suffer from a number of disadvantages that reduce their clinical utility. Problems include: 1) poor stability of the radionuclide/bisphosphonate chelate; 2) heterogeneity of the product with associated dosing issues; and 3) sub-optimal biodistribution properties leading to unwanted off-target tissue radiation exposure.

Many of these issues arise due to the fact that the radionuclide is chelated directly with the bisphosphonate entity thus reducing both the bone targeting ability and stability of the chelate. To circumvent these issues one approach is to attach a dedicated chelating group to the bisphosphonate backbone ("bifunctional bisphosphonates"). This separates the radionuclide chelating function from the bone targeting activity and overcomes many of the limitations of existing radiolabelled bisphosphonate agents. Early versions of such compounds have been reported in the literature but these examples were difficult to synthesise and formed enantiomers which may introduce unknown properties.

This opportunity relates to the discovery and synthesis of a series of novel and improved bifunctional bisphosphonates (2). The compounds are based on the approved bisphosphonate Alendronate linked to the chelating group dipicolylamine (DPA) or dithiocarbamate. These new agents chelate the commonly used radionuclides including ^{99m}Tc , ^{186}Re and ^{188}Re with very high efficiency and hence have both imaging and therapeutic applications.

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Biodistribution

The biodistribution of radiolabelled bisphosphonates is an important clinical factor as uptake outside of the bone leads to unwanted soft tissue radiation exposure. Some of the factors that can influence biodistribution are the bone affinity of the bisphosphonate and also any tendency to bind to serum proteins. Testing of one of our compounds ^{99m}Tc -DPA-Alendronate indicates much greater binding (>80% vs 40%) to hydroxyapatite (the key calcium salt in bone) and reducing binding to other calcium salts when compared to the currently used agent ^{99m}Tc -MDP (see Figure 1).

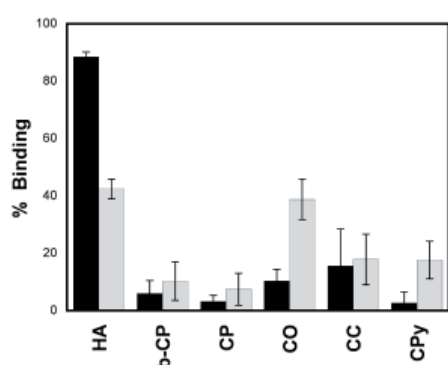


Figure 1: Binding study comparing the binding of ^{99m}Tc -DPA-Alendronate (black bars) and ^{99m}Tc -MDP (grey bars) to different calcium salts: Hydroxyapatite (HA); β -tricalcium phosphate (b-CP); calcium phosphate (CP); calcium oxalate (CO); calcium carbonate (CC) and calcium pyrophosphate (CPY).

In addition, ^{99m}Tc -MDP displays high levels of binding to serum proteins whereas our bifunctional bisphosphonates have virtually no serum protein binding activity. These two factors should help to target our bifunctional agents more effectively to bone than the traditional agents and hence limit unwanted soft tissue exposure. Initial *in vivo* studies confirm efficient bone targeting of our ^{99m}Tc -DPA-Alendronate compound with a bone to blood ratio of 867:1 compared to 244:1 for ^{99m}Tc -MDP.

In vivo imaging studies indicate efficient bone uptake of our compounds at sites of active bone remodelling (Figure 2). Bone metastases also represent sites of active bone metabolism/remodelling hence the utility of bisphosphonate agents in targeting such sites.

Stability and Homogeneity

Rhenium represents one of the most attractive radionuclides for therapeutic use due to its emission of high energy beta-particles. However, radiolabelled bisphosphonates are known to be unstable and rapidly degrade within the timespan of the agents' half life which reduces their potential effectiveness, especially in a therapeutic context. Loss of bisphosphonate radionuclide binding of over 50% has been reported for traditional agents within a 24hr timespan both *in vivo* and in

biological buffers. In contrast, data with our improved agents indicates that their stability is very high in serum with virtually no degradation observed at an 18 hr timepoint.



Figure 2: SPECT(colour)/CT(greyscale) image showing high uptake of ^{99m}Tc -DPA-Alendronate in bone tissue, particularly at the end of the long bones (sites of active remodelling).

It is anticipated that our improved agents will retain chelated Rhenium *in vivo* much more effectively than existing agents, translating to a higher and more sustained delivery of radiation to the bone metastases. This, combined with reduced off-target exposure as described above, should greatly increase the therapeutic index of such agents and make their clinical use attractive.

A further advantage is that both Rhenium and Technetium labelled versions of our agents are produced as single homogenous products with complete structural analogy between Rhenium and Technetium complexes, providing benefits in terms of clinical dosing and reproducibility. Unlike previously reported compounds, synthesis of our compounds is by a very simple single step reaction and the efficiency of radionuclide labelling is almost 100% (2). These chemical advantages combined with the biological benefits described above make these novel compounds attractive imaging and therapeutic agents

Intellectual Property

A composition of matter patent has been filed on the series of novel bifunctional bisphosphonate compounds.

References

1. Palmedo *et al.* J. Clinical Oncology 2003 21:2869-2875
2. Torres Martin de Rosales *et al.* Chem.Comm. 2009 32:4847-4849

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