



# Antagonist Licensing Opportunity

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## Antagonistic compounds for frizzled-1 and/or frizzled-2 receptors

- **Type of technology: platform → optimized leads**
- **Indication: (I) prevention and/or treatment of fibrosis resulting in malfunctioning of vital organs such as the heart (e.g. healing after myocardial infarct), lungs, kidney and liver, treatment of injured skeletal muscles, the attenuation of the aging process and cancer. (II) diagnostic use for molecular imaging of for instance the healing process after incidences such as myocardial infarction.**
- **Phase: Preclinical → optimized leads**
- First low molecular weight (LMW) antagonist
- Specific for frizzled-1 (Fzd-1) and -2 (Fzd-2)
- High bio-stability and near optimal receptor affinity

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### The challenge:

Antagonists of the Wnt/frizzled pathway may prevent fibrosis and prevent malfunctioning of vital organs as the heart, lungs, kidney and liver. Until now, the only way to intervene in the Wnt/Fzd pathway is at the level of the second messenger or other downstream signal elements, leading to aspecific blocking and interference in other signalling transduction cascades.

### Our solution:

Our scientists identified LMW (less than 21 Amino Acids) ligands that block the interaction between Wnt and Fzd-1 and/or Fzd-2 by occupying the receptor with a LMW ligand. These peptides provide a specific interaction with Fzd-1 and Fzd-2, and not Fzd-4 and Fzd-5, and can be used as a specific therapeutic tool in diseases which are in need of a downregulated Fzd-1 and -2 signaling. These LMW molecules may also be used as an imaging tool for such diseases.

### **Scientific background:**

There are 10 different Fzd receptors, that slightly differ in the variable cytoplasmatic part and the Wnt binding domain. When an agonistic ligand binds to the receptor, a signal transduction cascade gets activated.

Wnt proteins are very large proteins that tend to stick to the extracellular matrix and other biological and non-biological substances in a non-specific way. Because of its lack of specific binding, the natural ligand of the Fzd receptor is not suitable for visualization of the receptor.

Wnt signalling is required for different aspects of cardiac and vascular development, including myocardial specification, cardiac morphogenesis and cardiac valve formation as well as endothelial and vascular smooth muscle cell proliferation. Defective Wnt signalling can result in different vascular abnormalities in cancer. In the adult heart and blood vessels, Wnt signalling activity is quite low under normal conditions. However, this pathway is reactivated during pathological remodelling induced by pressure overload, in injured arteries and after myocardial infarction.

Myocardial infarction (MI) is characterized by the death of cells in the heart due to occlusion of a coronary artery. Some people will have a relatively good functioning heart after MI, whereas others have dilated hearts which function very badly.

It has been described that the well-healed heart contains more myofibroblasts in the infarcted area. Further research has shown that these hearts have increased levels of Fzd-1 and, especially, Fzd-2; whereas these receptors were mainly present on newly formed myofibroblasts. It has been proposed that these myofibroblasts give the heart the ability to preserve some of its

geometry and structure. Genetically modified animal models have shown that inhibition of Wnt signalling results in increased angiogenesis, better infarct healing and an attenuated hypertrophic response of the heart. This suggests that pharmacological inhibition of Wnt signalling could provide a good therapeutic strategy to prevent excessive cardiac and vascular remodelling. Antagonist of the Wnt/Fzd pathway may therefore prevent fibrosis and prevent malfunctioning of vital organs as the heart, lungs, kidney and liver.

Antagonists of the Wnt/Fzd pathway may also be useful in the treatment of injured skeletal muscles, which could be better healed after inhibiting the Wnt/Fzd signal transduction. Aging may also be slowed down by inhibition of the Wnt/Fzd signal transduction cascade. No antagonists for the Fzd receptors have been described before.

### **Preclinical data:**

The antagonist (UM206 antagonist) was tested for activity against the frizzled-1 and frizzled-2 receptors. The IC<sub>50</sub> value (concentration of antagonist at which 50% of the activity of the natural ligand is inhibited) is  $1 \times 10^{-10}$  M. When the antagonist was tested against frizzled-1, the IC<sub>50</sub> value was found to be  $1 \times 10^{-9}$  M.

When the peptides according to the invention were tested in a migration assay, the antagonist UM206 appeared to counteract the activity of the natural ligand Wnt3a. Where the natural ligand inhibits migration, the antagonist can block this effect completely. This indicates that administration of the antagonist ameliorates migration and therefore, has a beneficial effect on wound healing.

The antagonist UM206 has a half life of around 90 minutes in mice and rats, making it a good tool for visualization. Also for therapy, this long half life makes UM206 an excellent therapeutic composition. A steady state will be reached after +/- 10 hours.

The above data are examples, additional data is available.

### **CARIM**

The Cardiovascular Research Institute Maastricht (CARIM) of the University of Maastricht has expertise in a wide range of areas, ranging from molecular biology to population-based studies. Its goal is to focus on clinically important questions, integrating knowledge from molecule to patient.

CARIM is internationally renowned for its research in the Cardiovascular disciplines. In various reviews performed by the Royal Netherlands Academy of Arts and Sciences CARIM received the highest grading possible for its research and training program. Since 2007 BioMedbooster has started two new Ventures and closed nine license deals exclusively from CARIM-originated IP.

### **Inventors:**

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### **IP status:**

- Patent application filed

### **Licensing opportunity:**

- Available for licensing
- Additional information is available upon execution of a Confidentiality Agreement

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