



Agonist Licensing Opportunity

Agonistic compounds for frizzled-1 and/or frizzled-2 receptors

- **Type of technology: platform → optimized leads**
- **Indication: (I) treatment of diseases characterized by excessive fibrosis, e.g. cardiac hypertrophy, liver fibrosis, lung fibrosis and hypertrophic scarring of the skin after burning injuries; (II) diagnostic use for molecular imaging.**
- **Phase: Preclinical → optimized leads**
- First low molecular weight (LMW) agonist
- Specific for frizzled-1 (Fzd-1) and -2 (Fzd-2)
- High bio-stability and near optimal receptor affinity

The challenge:

Agonists of the Wnt/frizzled pathway may prevent fibrosis and prevent malfunctioning of vital organs as the heart, lungs, kidney and liver.

Unfortunately, no low molecular weight agonists for the frizzled receptors have been described before. 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.

Other means of intervention, are the use of purified natural ligands, which function as agonists. These natural ligands are however, difficult to purify and the bio-stability or plasma half life

is probably shorter than that of the LMW ligands identified by our scientists.

Our solution:

Our scientists identified LMW (less than 21 Amino Acids) ligands that mimick 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 an upregulated 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 frizzled 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 frizzled 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 cardiac and vascular abnormalities. In the adult heart and blood vessels, Wnt signalling activity is quite low under normal conditions. However, this pathway is reactivated during the pathological remodelling induced by pressure overload, in injured arteries and after myocardial infarction.

One application of therapeutic intervention of agonists for frizzled-1 and/or frizzled-2, that makes use of the agonists' markedly improved anti-fibrotic effect is for instance in cardiac hypertrophy induced by pressure overload. Applications of this agonist could also be found in diseases characterized by excessive fibrosis, e.g. liver fibrosis, lung fibrosis and hypertrophic scarring of the skin after burning injuries.

Preclinical data:

The agonist (UM206 agonist) was tested for activity against the frizzled-1 and frizzled-2 receptors. For that purpose, the cells were transfected with either Fz1 or Fz2 and the agonist was added in increasing amounts. The EC50 (amount of agonist that yields 50% of maximum activity) was measured. The EC50 for frizzled-2 was $2 \cdot 10^{-8}$ M and for frizzled-1 $1 \cdot 10^{-8}$ M.

The above data is an example, 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 clinched nine license deals exclusively from CARIM-originated IP.

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Licensing opportunity:

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

IP status:

- Patent application filed

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