MONOACYLGLYCEROL LIPASE (MAGL) INHIBITORS

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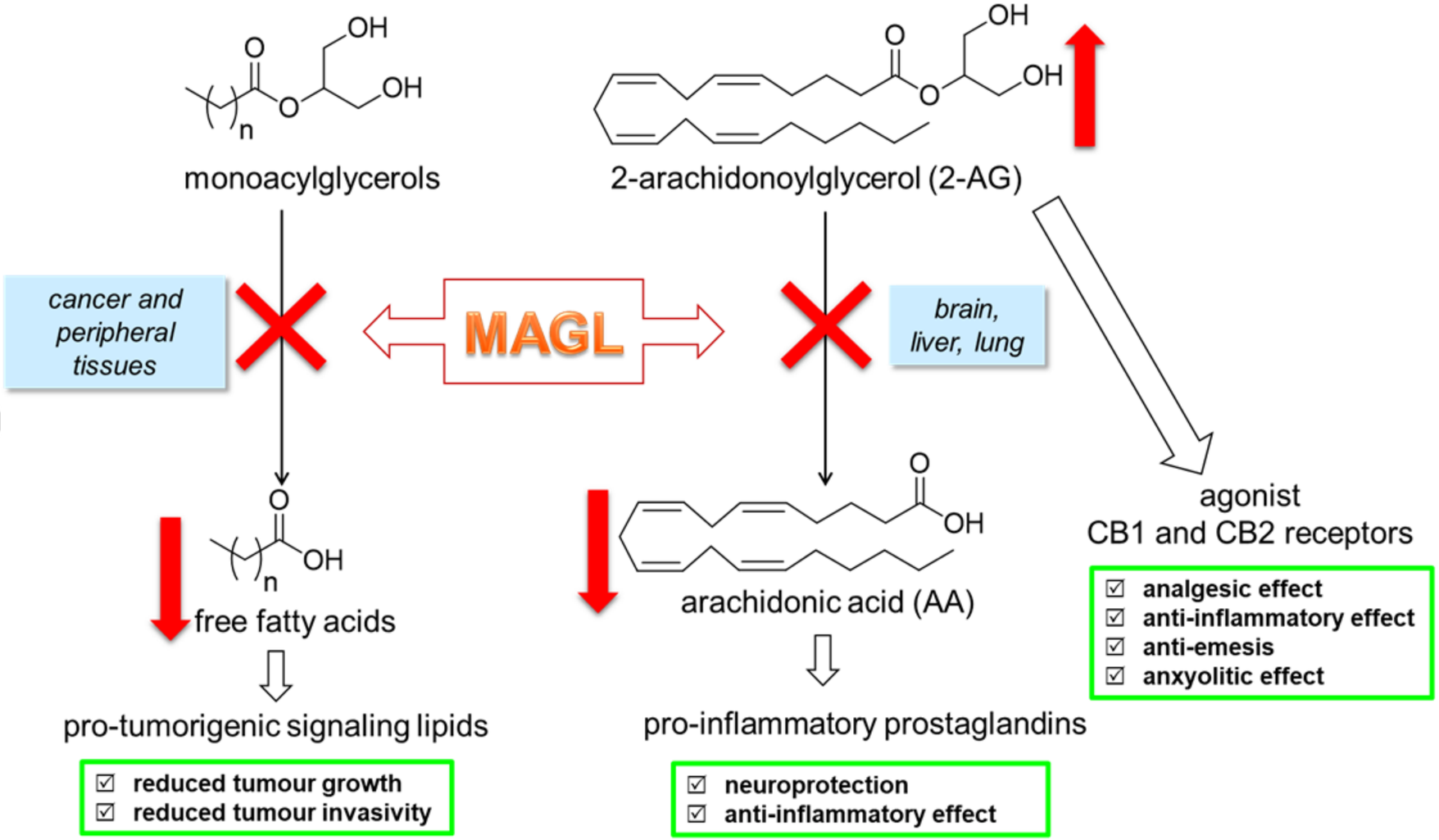
Invention

Inhibition of the enzyme monoacylglycerol lipase (MAGL), which is naturally present in many brain cells and involved in physio-pathological processes, has high therapeutic potential: pathologies of **neurodegenerative inflammation** and **tumors** could be treated with **reversible inhibitors of MAGL**, in order to reduce the side effects due to the use of irreversible inhibitors, which have been tested so far.

Monoacylglycerol lipase (MAGL) is a human enzyme of the endocannabinoid system involved in numerous physio-pathological processes (inflammation regulation, anxiety, immune modulation, motor coordination...). Its overexpression can be one of the cause of neuroinflammatory diseases and cancers. Inhibition of MAGL for therapeutic purposes has so far been studied with irreversible inhibitors, but turn off the enzyme's activity, leading to a progressive loss of therapeutic effect and addictive phenomena.

In contrast, the new patented compounds are based on a **potent reversible noncovalent mechanism of action**, which is useful for treating other **MAGL-mediated diseases** as well, such as neuroinflammation/degeneration, pain, multiple sclerosis/amyotrophic lateral sclerosis, Alzheimer's disease, and Parkinson's disease.

Drawings
& pictures



Industrial applications

The proposed technology may contribute to the development of an innovative therapeutic tool to treat:

- severe pathological conditions of **neurodegenerative inflammation**,
- various types of **tumors**.

Possible developments

The patented class of compounds has a r**eversible mechanism of action**, which is advantageous in terms of **safety profile** compared with the currently developed irreversible inhibitors.
Chronic administration of irreversible inhibitors has, in fact, been associated with adverse effects *in vivo*, such as downregulation of some receptors and physical dependence. Therefore, recent studies focused on the development of reversible inhibitors, that lack of these undesirable effects and have an **optimal pharmacokinetic profile**.

The high efficacy of the patented compounds has been tested on various cancer cell lines (i.e., colorectal, breast, and ovarian cancer). Ongoing studies aim to increase the efficacy of these reversible, noncovalent MAGL inhibitors, including further investigation of SAR and development of additional structural analogs to improve their pharmacological properties.

The patented compounds could be used as active ingredients for drug development against numerous neurodegenerative diseases, which still lack effective pharmacological treatment.

The inventors are interested in future collaborations to increase the technological maturity of the invention and expand the supply of innovative drugs for the treatment of cancer or neurodegenerative diseases.

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