Gleevec for pain

By Lauren Martz, Staff Writer

Researchers at **The University of Texas MD Anderson Cancer Center** have found a potential new use for **Novartis AG**'s Gleevec imatinib cancer drug—reducing tolerance to opioid analgesics.[1] Gleevec prevented and reversed morphine tolerance in rats, but it is still unclear whether the molecule's safety profile would be suitable for the pain indication.

Novartis is not pursuing the new indication, but the academics are pressing forward and plan to submit an IND for a reformulated version of the drug within the next year.

Opioid analgesics, including morphine, lose potency over time as patients become tolerant to the analgesic effects, resulting in the need for higher doses. This may contribute to addiction and exacerbate side effects such as respiratory depression, constipation and cognitive changes including depression and sedation.

There has been no shortage of research on ways to block tolerance. For example, protein kinase A (PKA), PKC and NMDAR have been identified as potential contributors to the development of opioid tolerance.[2–4] What has been lacking is small molecule inhibitors against those targets.

Now, a group led by Howard Gutstein, associate professor of anesthesiology and biochemistry at MD Anderson, has added platelet derived growth factor receptor B (PDGFRB; PDGFR1; CD140B) to the list of potential targets for opioid tolerance and has used Gleevec to test the effects of inhibiting the target.

Gleevec is a BCR-ABL tyrosine kinase inhibitor that nonselectively targets PDGFRB. It is approved to treat chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors.

His group had hints about PDGFRB's role in tolerance from a pair of studies from a **University of Minnesota Medical School** team led by Kalpna Gupta, associate professor of hematology, oncology and transplantation.

In 2006, the Minnesota team showed that morphine activates PDGFRB, as well as other receptor tyrosine kinases, in endothelial cells.[5] Six years later, the researchers found that morphine also activated the receptor in vascular pericytes *in vitro* and in mice.[6]

In rats, Gutstein and colleagues showed that intrathecal morphine increased PDGFRB activation by 47%. That effect was blocked by the team's reformulated version of imatinib, which has better blood brain barrier penetration than the parent compound.

Intrathecal or subcutaneous doses of the drug also prevented or reversed morphine tolerance, whereas vehicle control had no effect. Gleevec alone did not cause or prevent analgesia.

Moreover, Gleevec did not prevent tolerance to the nonopioid analgesic clonidine, suggesting its effect is specific to opioid therapeutics.

Because Gleevec hits multiple targets, the researchers wanted to be sure its activity on PDGFRB was causing the observed effects. Thus, the team treated rats with morphine plus an antibody against PDGFRB. The molecule produced a reversal of morphine tolerance similar to that seen using Gleevec.

Finally, Gutstein's group showed that activating PDGFRB with its ligand, platelet derived growth factor BB (PDGFBB), reversed the effects of PDGFRB inhibition by Gleevec and restored and further induced tolerance. These findings suggest that morphine-induced increases in PDGFRB signaling contribute to opioid tolerance and that inhibiting the signaling could prevent tolerance.

Data were published in *Nature Medicine*.

"A number of other targets have shown similar promise in reducing opioid tolerance, including PKA and several PKC isoforms, as well as a number of different G protein–coupled receptors," said John Violin, head of biology at **Trevena Inc.** "This study adds PDGFRB and imatinib to that list, and also nicely illustrates the mechanism whereby that target is engaged. This discovery may help the field better understand the molecular mechanisms of tolerance."

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Therapeutic strategy

Gutstein told *SciBX* his team has performed pharmacokinetic and pharmacodynamic studies of the reformulated Gleevec and hopes to submit an IND within the next year.

"To be used therapeutically, one would need to combine a PDGFR antagonist with the analgesic. This introduces significant complexities classically associated with combination therapies such as determining the correct dose for both agents and formulating both agents to allow them to be used together," said Violin. "There is also the potential for new or augmented side effects due to combination therapy."

Trevena's TRV130, a G protein–based μ-opioid receptor (OPRM1; MOR) ligand, is in Phase I testing to treat postoperative pain. TRV130 is designed to stimulate the G protein–coupling mechanism that induces analgesia without stimulating the arrestin-β–coupling mechanism that causes respiratory and GI side effects.

Violin said a key question is whether "blocking tolerance will increase the incidence of adverse events more than it will increase analgesia." He said the researchers also need to consider Gleevec's known side effects, which include edema and fluid retention.

He said that instead of using Gleevec, a better approach to reducing

opioid tolerance could be to start from scratch and design a specific inhibitor of PDGFRB.

Gutstein, however, doesn't think this will be necessary. "Imatinib is well-tolerated in patients, so I think it would not be necessary to develop a more specific antagonist," he said.

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Gupta thinks Gleevec would be an ideal therapeutic for cancer patients with breakthrough pain. These patients, who are already being treated with imatinib, could experience the added benefit of reduced morphine tolerance.

Javier Garzón, head of neuropharmacology at the **Cajal Institute**, which is affiliated with the **Spanish National Research Council**, thinks PDGFRB is unlikely to be the ideal target in the path of morphine tolerance. He said the process of morphine tolerance can be manipulated at many points, and that the team should identify the target that is furthest upstream in the pathway.

Novartis spokesperson Julie Masow said the company is "aware of the report in *Nature Medicine* that a reformulation of Gleevec imatinib may improve the effectiveness of narcotic medications. Novartis was not involved in this research and has no plans to conduct studies of Gleevec in this setting."

Gutstein said MD Anderson has filed for a patent covering the work. The IP is available for licensing.

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