Licensing opportunity
Oral CXCR4 Antagonists
Potential in oncology, tissue injury/repair, and stroke

Mechanism of Action: CXCR4 Antagonist
Proposed Indications: Single/Combination agent post radiation in Glioblastoma (GBM)

Other Indications: Head and Neck Cancer, other radiation treated tumors (breast, lung, etc.)
Chronic Leukemias (CLL, CML), Prevention/treatment of metastases (lymph nodes, lung, liver, bone), Stroke, and Ischemia Reperfusion Injury

Patent Protection: The portfolio comprises a number of patent families with nominal expiration dates ranging from 2022-2027

Route of Administration: Oral
Development Phase: One compound in Phase I (others in preclinical)

Competition: Other CXCR4 antagonists, none approved (most advanced in Ph1/2, Majority of other compounds in development are injectable)

1. RATIONALE AND BACKGROUND

Chemokines, small pro-inflammatory chemo-attractant cytokines that bind to specific G-protein–coupled receptors (GPCRs) present on the plasma membranes of target cells, are the major regulators of cell trafficking. Some of them have also been reported to modulate cell survival and growth. The perturbation of the SDF-1–CXCR4 axis, by mobilizing agents, is essential for the egress of hematopoietic stem/progenitor cells from bone marrow (BM) into peripheral blood (PB). In glioblastoma multiforme, pharmacologic inhibition of HIF-1 or of the SDF-1/CXCR4 interaction prevented the influx of Bone Marrow Derived Cells (BMDCs), primarily CD11b+ myelomonocytes, and the post-irradiation development of functional tumor vasculature, resulting in the abrogation of tumor regrowth (Kioi, 2010). The SDF-1–CXCR4 axis may influence the biology of tumors and direct the metastasis of CXCR4+ tumor cells via chemo-attraction to organs that highly express SDF-1 (e.g., lymph nodes, lungs, liver, or bones). Supporting this notion, it has been recently reported that several CXCR4+ cancers (e.g., breast, ovarian, prostate cancers, rhabdomyosarcoma, and neuroblastoma) metastasize to the bones from the bloodstream in an SDF-1–dependent manner. In other settings, such as stroke (or other ischemic injury), there are increased levels of SDF1 in the ischemic region, which leads to an accumulation of cells and mechanisms that perpetuate inflammation. By blocking the SDF1/CXCR4 pathway, functional recovery has been improved, likely through preventing immune cells from reaching the ischemic regions.
2. MARKET

Glioblastoma multiforme (GBM) is the most common and most aggressive malignant primary brain tumor in humans, involving glial cells and accounting for 52% of all functional tissue brain tumor cases. In the US, there are approximately 12,000 incident patients per year, and the majority (nearly 9,000) of them receive radiation as their primary treatment. In the EU5, the numbers are similar, with 15,000 incident patients, and approximately 11,000 receiving radiation treatment. Prognosis for these patients is poor, with median survivals of <6 months.

3. COMPOUND PROFILE

- Multiple Sanofi compounds, small molecules, have shown promise as selective antagonists of CXCR4.
  - AMD 11070 – This compound has been in the clinic in phase I studies, in HIV patients but was put on clinical hold due to findings in long term rat and dog toxicology studies (hepatotoxicity and retinal bleeding).
  - AMD 12118 – This compound is at the preclinical stage, with some toxicology data available (additional GLP tox work may be required for IND) no clinical trial experience to date.
  - AMD 11814 and AMD 13073 – Both compounds have been identified as promising backups. Minimal toxicology data have been generated on these compounds.
  - Additional compounds are in the chemical library.

- Clinical Experience to Date:
  - **AMD11070-1001 (XACT)** - Multicenter, Dose-Finding Safety and Activity Study of AMD11070 In HIV-infected Patients Carrying X4-Tropic Virus. Dosing was BID for 10 days.
  - **AMD11070-1002 (XIST)** - A Study of the Pharmacokinetic Interaction between AMD11070 and Substrates of CYP3A4 and 2D6 Enzymes in Healthy Volunteers. Dosing was BID for 9 days.

- Regulatory interactions re: AMD11070:
  - In November 2006, the FDA was notified that hepatotoxicity and retinal changes were seen in nonclinical studies and all clinical sites were advised to suspend screening and enrollment, which resulted in the studies being placed on clinical hold.

- CXCR4 antagonist data in a preclinical GBM Model:
  - When a CXCR4 antagonist (in this case Mozobil, an injectable CXCR4 antagonist currently marketed by Sanofi) is given continuously for 21 days post radiation treatment in a mouse model, tumor regrowth is completely prevented.

Therapeutic effect of blocking the interaction of SDF-1 with CXCR4 after whole brain irradiation.

(A) Growth curves of i.c. U251 early tumor model after fractionated irradiation (5 daily doses of 2 Gy starting on day 11 after transplantation). *P < 0.05. (B) BLI images after fractionated irradiation treated with or without MozobilFrom Kioi, et al. JCI 2010
4. PRELIMINARY SAFETY AND PHARMACOKINETIC PROFILE

AMD11070 advanced to a Phase Ib/IIa dose-finding safety and activity study in HIV-infected subjects in November 2004 but was placed on clinical hold following findings in a 3-month dog toxicity study with AMD11070 free base. The study reported histopathology findings of inflammation, necrosis and pigmentation in the liver (SN0037; 9/29/06). In the human trial (10 days of BID administration), AMD11070 was safe and well-tolerated; all side effects were reversible and non-dose related. Elevation in bilirubin (n=2) and lipase (n=4) were possibly related to dosing. The PK profile suggests rapid oral absorption with bi-exponential elimination, large Volume of distribution, high clearance, terminal half-life of 11-16 hours, mixed-order pharmacokinetics (super-proportional increase in AUC at doses > 200 mg, significant reduction in drug exposure in the presence of food).

5. VALUE PROPOSITION

➢ In GBM, there is a high unmet medical need. Short survival (<6 months) with limited treatment options available.
➢ Conventional therapies attack tumor cells, but none attempts to manage trafficking and homing of normal cells (specifically Bone Marrow Derived cells; for example CD11b+ cells), which can promote recurrence.
➢ If successful, this therapeutic modality could potentially be extended to other radiation-treated primary tumors, including head and neck, breast, and lung as potential examples.
➢ There are a number of other therapeutic areas that could be explored with CXCR4 antagonism.

6. REFERENCES

Combination of drug therapy in acute lymphoblastic leukemia with a CXCR4 antagonist, R.Parameswaran et al., 2011, Leukemia, August 25(8):1314-1323.

7. CONTACTS

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