BIOBUSINESS BRIEFS

DEAL WATCH

Dipping into Incyte's JAK-pot

Incyte has entered into two large licensing deals for their JAK1/JAK2 inhibitors INCB28050 and INCB18424. In late December 2009, the worldwide rights to INCB28050, which is in mid-stage trials for rheumatoid arthritis, were acquired by Eli Lilly for US$90 million upfront, with up to $665 million in potential milestone payments. This followed soon after a deal in which Novartis acquired ex-US rights to INCB18424 — which is in Phase III trials for myelofibrosis — as well as the MET inhibitor INCB28060, for $150 million upfront and up to $1.1 billion in potential milestone payments.

JAKs are a family of intracellular non-receptor tyrosine kinases that transduce cytokine-mediated signals via the JAK–STAT pathway. More than 20 clinical trials are currently investigating JAK inhibitors for treating diseases including autoimmune/inflammatory disorders, cancer and several myeloproliferative disorders (TABLE 1).

Gain-of-function mutations in JAK2 have been found in a substantial proportion of patients with myeloproliferative disorders, including myelofibrosis, a debilitating disease that currently has no effective medications, as well as in patients with polycythaemia vera and essential thrombocythaemia. "The potential causal role of JAK2 in these diseases, coupled with the attractiveness of JAK2 as a target for developing selective, potent and orally bioavailable molecules, resulted in great enthusiasm to target JAK2," says Srdan Verstovsek, Associate Professor at the MD Anderson Cancer Center, Texas, USA. "Myelofibrosis is also a highly inflammatory state associated with unchecked production of inflammatory cytokines, and it seems that inhibiting JAK1 at the same time could add to the therapeutic effect by further inhibiting cytokine signalling. In addition, targeting JAK1 in addition to JAK2 might counteract the apparent weakening of the antiproliferative effect of JAK2 inhibition in the presence of cytokines."

For rheumatoid arthritis, the current leading disease-modifying drugs, which inhibit the cytokine tumour necrosis factor, require parenteral administration. "Using JAK inhibitors in rheumatoid arthritis and other autoimmune diseases has the advantage that they are oral drugs and so can be stopped if patients get infections, and the dose can be altered more quickly," says John O'Shea, Scientific Director of the Molecular Immunology and Inflammation Branch at the National Institute of Musculoskeletal and Skin Diseases, National Institute of Health, USA. O'Shea also thinks that agents with the capacity to block multiple cytokines might be more efficacious than drugs that block a subset. "Inhibiting JAK1/2 has the advantage of targeting multiple cytokine receptor families, but the key question for this class of drugs is whether a higher degree of specificity for individual JAKs is desirable, or whether pan-JAK inhibitors will have better efficacy," he says. "Related to this, will JAK inhibitors be more effective in combination with existing drugs, or will this result in more infections?"

"Questions also remain related to the significance of the relatively uncharacterized role of JAKs in innate immunity and the selectivity of some of the inhibitors," notes Matthias Gaestel, Hannover Medical School, Germany. "Nevertheless, in Phase II trials so far, oral JAK inhibitors have been well tolerated, with no major side-effects reported".

Table 1 | **Selected JAK inhibitors in clinical development**

Compound (Developer)	Target(s)	Selected indications (Phase)
INCB18424 (Incyte/Novartis)	JAK1/2	Myelofibrosis (Phase III); thrombocythaemia, polycythaemia vera, multiple myeloma, prostate cancer, rheumatoid arthritis, psoriasis‡ (Phase II)
CP690550 (Pfizer)	JAK3	Rheumatoid arthritis (Phase III), psoriasis (Phase II), inflammatory bowel disease (Phase II)
INCB28050 (Incyte/Lilly)	JAK1/2	Rheumatoid arthritis (Phase II)
AZD1480 (AstraZeneca)	JAK2	Myelofibrosis, polycythaemia vera, thrombocythaemia (Phase II)
TG101348 (TargeGen)	JAK2/FLT3/RET	Myelofibrosis (Phase II)
SB1518 (S*BIO)	JAK2	Chronic idiopathic myelofibrosis (Phase II)
CYT387 (Cytopia)	JAK1/2	Myelofibrosis, polycythaemia vera, thrombocythaemia (Phase II)

‡Topical formulation.