S100A4 NEUTRALISING ANTIBODY

• Neutralising antibody that recognises both human and mouse S100A4
• In vivo efficacy demonstrated
• Broad utility in oncology and inflammatory disease indications

COMMERCIAL OPPORTUNITY
The anti-S100A4 antibody comes with a package of data demonstrating potent inhibitory action against S100A4 in vitro and in vivo in a cancer xenograft model. In addition to utility in a range of common cancer types, there are clear links between S100A4 and a number of inflammatory indications, such as rheumatoid arthritis and psoriasis, where specific inhibition of S100A4 may also be of value. CRT seeks a licensee or collaborative partner for the further development of this anti-S100A4 antibody. There is potential for “first in class” S100A4-specific therapies.

THE TECHNOLOGY
A lead anti-S100A4 mouse monoclonal antibody (6B12) has been identified by a group led by Professor Eugene Lukanidin, a world leader in S100A4 biology [1]. Importantly, this antibody is S100A4 selective – it does not cross-react with other S100 family members and no binding was visualised in S100A4 knockout cells. Furthermore, the antibody binds both mouse and human S100A4, and can detect the protein in intact cells or whole cell lysates. Epitope mapping for the 6B12 antibody has defined the binding region as a functional domain in the C-terminal portion of S100A4. This region encompasses the second EF-hand (calcium-coordination) and part of alpha helix IV; residues in these areas are known to be involved in forming the hydrophobic cleft, which binds to target proteins and is involved in self-association.

The antibody is highly effective against cellular S100A4 activity as demonstrated by the ability of the antibody to inhibit S100A4-induced invasion of both mouse embryonic and human mammary fibroblasts in a 3D Matrigel matrix. Furthermore, the antibody significantly reduced T cell invasion into a S100A4-positive fibroblast monolayer in vitro.

IN VIVO EFFICACY
The ability of the anti-S100A4 antibody to block tumour growth and metastasis was assessed in a mouse model of spontaneous metastasis – xenografted CSML100 mouse mammary carcinoma cells that metastasize to the lungs [1]. Three times weekly treatment with the antibody resulted in a significant reduction in metastatic burden (Figure 1A) and a significant increase in the number of mice that were metastasis-free. There was no significant toxicity associated with antibody administration in these studies.

A consequence of the enhanced expression and release of S100A4 from tumour and stromal cells is the recruitment of cells of the immune system. One potential mechanism of action by which the anti-S100A4 antibody decreases metastatic burden is through its ability to inhibit T cell attraction to the tumour site (Figure 1B). This could compromise the production of T cell derived factors, which would otherwise stimulate metastatic spread of the cancer cells.

Legend overleaf
Figure 1. Anti-S100A4 antibody 6B12 reduces metastatic burden in mice (A) and decreases the infiltration of T lymphocytes into the tumour in vivo (B).

OTHER APPLICATIONS
In addition to being developed as a naked antibody cancer therapeutic, the anti-S100A4 antibody has other potential therapeutic and diagnostic applications:

- Treatment of inflammatory diseases: S100A4 expression is increased in patients with rheumatoid arthritis and psoriasis, indicating that the anti-S100A4 antibody could also be developed as a therapeutic for certain inflammatory diseases. Indeed S100A4 blocking antibodies have already been shown to reduce psoriatic pathology in vivo [2].

- Tumour targeting: there is potential to use the antibody to target other therapeutics to the tumour microenvironment.

- Diagnostic: the antibody could be used for diagnostic or prognostic testing by tracking the expression level of S100A4.

BACKGROUND AND THERAPEUTIC RATIONALE
S100A4 (Mts1) is a member of the S100 family of EF-hand Ca-binding proteins. Upon binding calcium, the S100A4 dimer undergoes a marked conformational change revealing two hydrophobic pockets that interact with multiple intracellular targets, such as non-muscle myosin or the tumour suppressor protein p53. Thus S100A4 has the ability to interact with and regulate multiple cell signalling pathways, such as apoptosis, proliferation, motility, invasion, and angiogenesis [3].

Whereas the normal expression pattern of S100A4 is limited, S100A4 expression is elevated in a range of cancer types as well as rheumatoid arthritis, psoriasis, kidney fibrosis, liver fibrosis, cardiac and lung disease [4, 5]. Furthermore, high S100A4 expression has been identified as a significant marker for poor prognosis in several cancer types (including breast, ovarian, pancreatic, gastric, gallbladder and non-small cell lung cancer) and linked to an elevated incidence of metastasis [3].

The link between S100A4 and metastasis was first described by Professor Lukanidin. Subsequently the role of S100A4 in metastasis formation and tumour progression has been well validated, both in vitro and in vivo. Most strikingly S100A4-deficient mice, which are otherwise viable, exhibited significant impairment in tumour uptake and metastasis [6]. S100A4 also plays an important role in the maintenance of cancer stem cells - knockdown of S100A4 reduced the self-renewal capability, stemness and tumorigenic properties of cancer initiating cells [7]. Furthermore, knockdown of S100A4 in two cancer cell lines reduced their tumour forming efficiency in vivo [7, 8]. As such, a neutralizing antibody to S100A4 could be a potential therapeutic option to block tumour progression and metastasis, and hence enhance survival.

S100A4 has been shown to be expressed in tumour cells but is also secreted by tumour-associated stromal cells, resulting in its accumulation in the tumour microenvironment. This extracellular form of S100A4 is increasingly being recognised as a key player in metastasis, for example S100A4 has been shown to stimulate recruitment of immune cells to the site of the growing tumour, EGFR dependent signalling, production of MMPs and act as an angiogenic factor [4, 9, 10]. Importantly, extracellular S100A4 could be easily accessed by an antibody-based therapeutic.

INTELLECTUAL PROPERTY
A patent application has been filed protecting the lead anti-S100A4 antibody along with the novel epitope.

REFERENCES

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