

# ADDITIONAL INFORMATION

## MIDKINE INTELLECTUAL PROPERTY PORTFOLIO



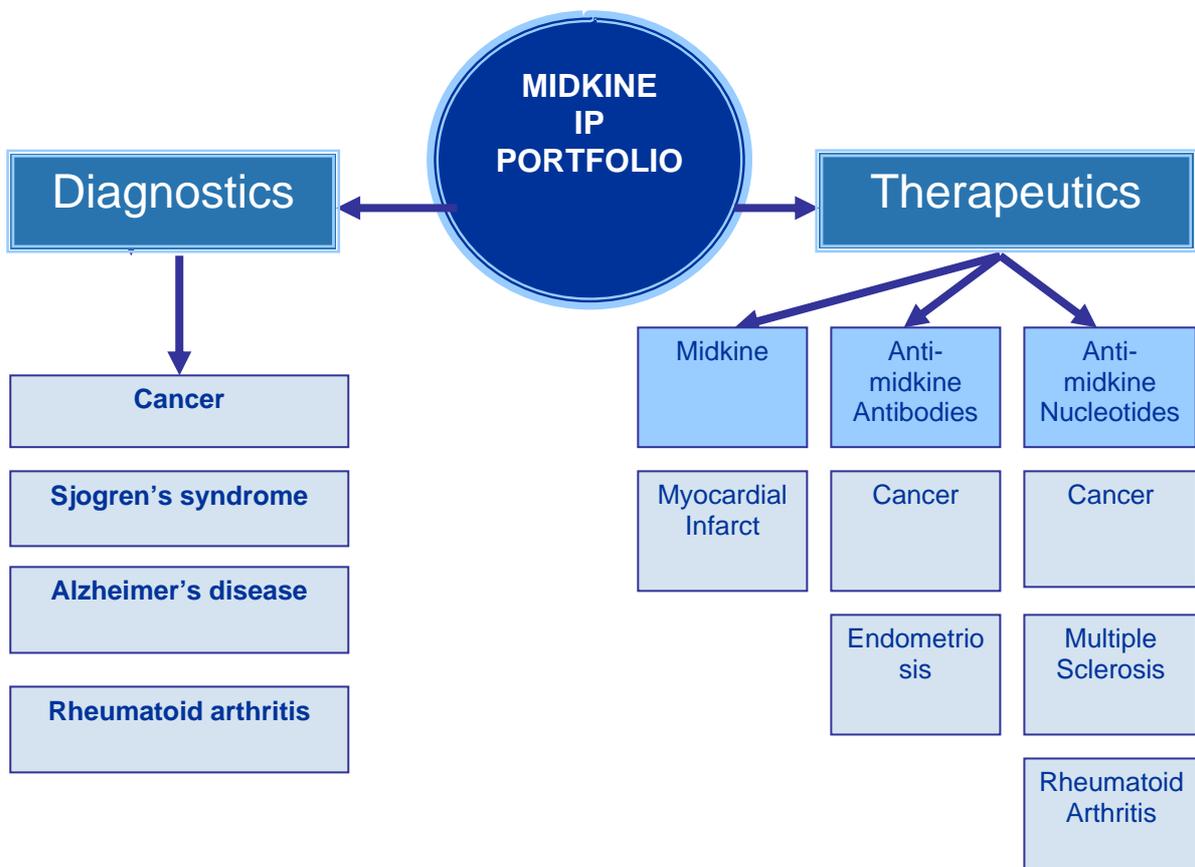
This Additional Information should be read in conjunction with the Investor Presentation on Midkine and the Notice of Meeting which were both released to the market earlier in May 2008. This paper should assist Shareholders in their assessment of the proposed acquisition of the Midkine Intellectual Property Portfolio by providing additional technical, market related and commercial information. Please direct any enquiries to Maria Halasz at Medical Therapies Limited.

# 1. Midkine Intellectual Property Portfolio

Medical Therapies and Cell Signals signed an Intellectual Property Agreement on 16 April 2008 affecting the transfer of all patents, patent applications, know-how, technical and manufacturing information and all other intellectual property developed by Cell Signals on midkine (Midkine Intellectual Property Portfolio or Midkine IP Portfolio).

The Intellectual Property Portfolio relates to the midkine protein, as well as anti-midkine agents (antibodies, RNAi and antisense oligonucleotides) in therapeutic and diagnostic applications. The Midkine IP Portfolio includes 28 patents, more than 120 anti-midkine antibodies and hybridomas for the production of antibodies, midkine and ELISA (Enzyme-linked Immunosorbent Assay) kits for midkine detection for use in diagnostics (see Figure 1 below). This paper provides additional information to assist shareholders and interested parties in their assessment of this complex and important intellectual property asset.

**Figure 1** The Midkine Intellectual Property Portfolio includes **DIAGNOSTIC** and **THERAPEUTIC** applications of the midkine protein, anti-midkine antibodies and anti-midkine nucleotides



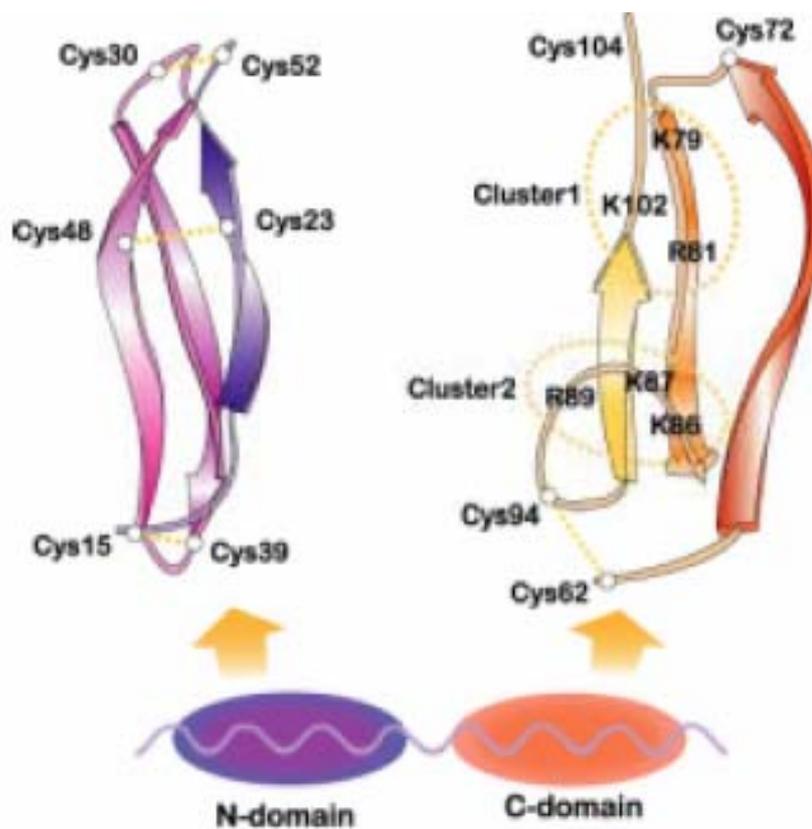
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## 1.1 Midkine protein

Midkine (see Figure 2) is a small protein expressed during oncogenesis, as well as at the onset of autoimmune and inflammatory diseases. Since its discovery in 1988 a large body of evidence has been accumulated in relation to the use of midkine for the diagnosis and treatment of various tumors as well as inflammatory and autoimmune diseases.

High levels of midkine can be detected in the blood from the onset of cancer, allowing early diagnosis of the disease and improved prognosis for patients. Detection of midkine, alongside other markers, may also help with the diagnosis of Rheumatoid Arthritis, Sjogren's syndrome and Alzheimer's disease. Extensive *in vitro* and preclinical data supports the use of midkine for the prevention and treatment of heart damage during myocardial infarct.

**Figure 2** Midkine is a two domain low molecular weight (13kD) growth factor-like protein with roles in anti-apoptosis, cell migration, neo-angiogenesis and cell growth



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## 1.2 Patents

A portfolio of 28 patents and patent applications covers the use and manufacture of midkine and anti-midkine reagents for a wide range of diagnostic and therapeutic applications. Table 1 below includes a list and brief description of key patents and patent applications, forming part of the intellectual property acquired by MTY.

**Table 1 KEY PATENTS AND PATENT APPLICATIONS**

| Application No.    | Title  | Country            |                |
|--------------------|--|--------------------|----------------|
|                    |  | Granted            | Pending        |
| PCT JP98/03161     | AGENTS COMPRISING MIDKINE OR ITS INHIBITORS AS ACTIVE INGREDIENTS                                      | AU,EU,KR           | CA, CN, JP, US |
| PCT /JP98/04299    | PREVENTIVES OR REMEDIES FOR ISCHEMIC DISEASES  | AU, EU, KR, CN     | CA, JP, US     |
| PCT /JP99/04332    | MASS SECRETION/EXPRESSION SYSTEM OF TRUE MK FAMILY PROTEIN   | US                 |                |
| PCT /JP99/04550    | PREVENTIVES/REMEDIES FOR ARTERIOSCLEROSIS AND POST-PTCA REANGIOSTENOSIS                                | AU, CN, KR, US     | CA, EU, JP     |
| PCT /JP00/06147    | EARLY CANCER TUMOR MARKER  | AU, CN, KR, US, EU | CA, JP         |
| PCT /JP2004/002888 | PREVENTIVE FOR ADHESION FOLLOWING ABDOMINAL SURGERY  |                    | EU, JP, US     |
| PCT /JP2005/022354 | COMPOSITION FOR TREATING OR PREVENTING MYOCARDIAL DISORDER OR HEART FAILURE                            |                    | EU, JP, US     |
| PCT /JP2006/310375 | PHARMACEUTICAL COMPOSITION FOR VASCULAR OCCLUSIVE DISEASE  |                    | EU, JP, US     |
| PCT /JP2006/322659 | METHOD FOR TREATMENT OR PREVENTION OF DISEASE ASSOCIATED WITH FUNCTIONAL DISORDER OF REGULATORY T CELL |                    | WO             |
| PCT /JP2007/001238 | ANTIBODIES RECOGNIZING C-DOMAIN OF MIDKINE   |                    | WO             |
| PCT /JP2007/070441 | PHARMACEUTICAL COMPOSITION FOR OBLITERATIVE VASCULAR DISEASE   |                    | WO             |
| PCT /JP2008/000815 | AGENT FOR ACTIVATING NITRIC OXIDE SYNTHASE   |                    | WO             |

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### **1.3 Anti-Midkine antibodies**

The Midkine IP portfolio includes more than 120 anti-midkine antibodies which will be used for the diagnosis of cancer and autoimmune diseases. They will be further developed targeting the treatment of solid tumors, anti-inflammatory conditions and autoimmune diseases as further discussed in sections 2 and 3 of this document.

### **1.4 Proprietary reagents**

All the reagents owned by Cell Signals will be transferred to MTY once settlement takes place. These include midkine, hybridomas for the production of anti-midkine antibodies and ELISA kits for midkine detection.

### **1.5 Research data, technical information and know-how**

A large body of experimental data has been produced by the researchers at Cell Signals over the past 12 years in relation to midkine. The production of the midkine protein and subsequent development of anti-midkine antibodies, its mechanism of action, use as a diagnostic, its role in the development of a number of conditions and potential use in a range of therapeutic applications forms part of a valuable data package MTY will own following settlement.

## **2 Midkine Therapeutics**

### **2.1 Treatment of myocardial infarct using midkine**

Some 1.5 million<sup>1</sup> people will suffer from acute myocardial infarct (or heart attack) this year in the US alone and approximately 30% of them will die. Indeed in Australia 48,000 people died from acute heart conditions in 2004<sup>2</sup>, most of these preventable. Current treatments focus on surgical procedures and medications that help the heart pump better and regulate blood pressure.

Experiments conducted in animal models show that midkine helps reduce damage to the heart muscle (Figure 3, 4 and 5 below). With a significant unmet medical need for treating the damage to the heart as a result of a myocardial infarct, midkine is potentially a first-in-class agent and a breakthrough therapeutic approach.

Midkine has been tested for both the prevention and treatment of damage to the heart, in particular left ventricular fibrosis. In a pig model of myocardial infarct, a reduction of infarct size, systolic/diastolic dysfunction and mortality rate was

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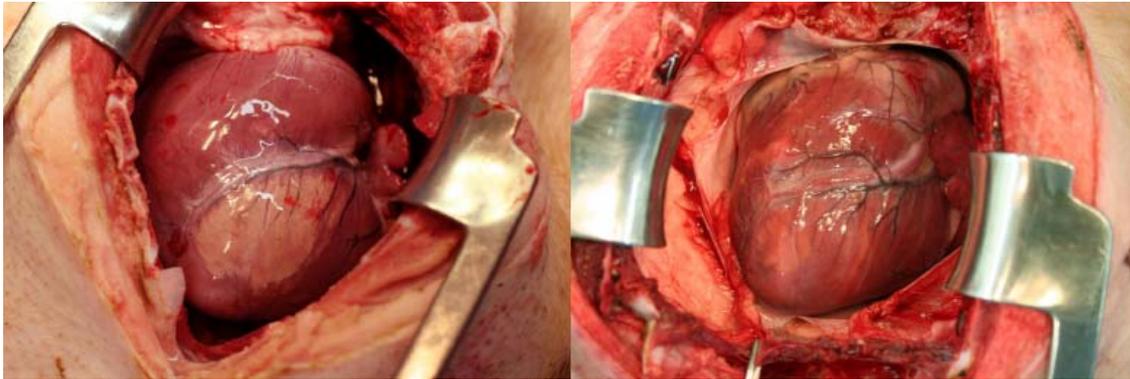
<sup>1</sup> National Institute of Health

<sup>2</sup> Heart Foundation (Australia)

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observed 24hr after a single intracoronary injection of 5µg/kg of midkine. In this trial the mortality rate has showed a three-fold reduction when using midkine from 33% (4/12) in the controls to 11% (1/9) in animals treated with midkine. Importantly, a single injection of midkine caused no acute hypotension, a limitation when using other growth factors.

**Figure 3 Pig model of myocardial infarct**

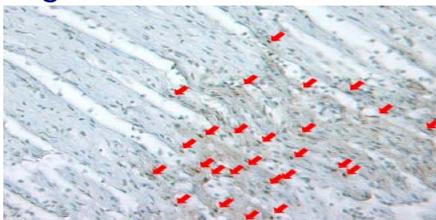


**Control** animal 24hr after acute myocardial infarct. The light coloured part is the extensively damaged left ventricular area. The mortality rate of the control group was 33% or 4 in 12 pigs.

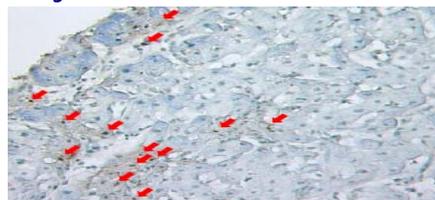
**Midkine** treated pig 24hr after acute myocardial infarct with reduction in light coloured areas which indicate a reduction of left ventricular damage. The mortality rate of the midkine treated group was 11% or 1 in 9 pigs.

Histopathological analysis of heart tissue taken from mice, using a mouse model of acute myocardial infarct, showed that midkine reduces cell death (Figure 4 Apoptosis) and promotes the growth of blood vessels (Figure 5 Angiogenesis) in mice treated with midkine.

**Figure 4 APOPTOSIS: Mouse model of myocardial infarct**



**Control** – heart tissue sections show extensive cell death within 24 hours following myocardial infarct



**Midkine treated mice** – heart tissue sections show that a single dose of midkine significantly reduced cell death following myocardial infarct

**Figure 5 ANGIOGENESIS: Mouse model of myocardial infarct**



**Control** – Few blood vessels are formed in the heart muscle following myocardial infarct



**Midkine treated mice** – Blood vessel formation improved significantly after administering a single dose of midkine following myocardial infarct

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## 2.2 Anti-midkine treatment for cancer

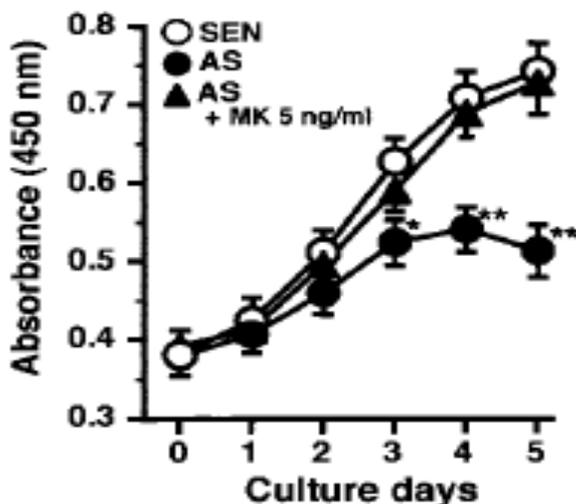
More than 11 million new cases of cancer are diagnosed globally each year. Current treatments include surgery, chemotherapy, radiotherapy and targeted therapies that are specifically directed at molecules particular to cancer cells. In most cases treatment regimes include a complement of several approaches to improve patient outcomes.

It is predicted that by 2012 the spending on cancer therapeutics will reach US\$45 billion annually. Of all the available regimes targeted therapy, such as Herceptin<sup>3</sup> for metastatic breast cancer, appears to be one of the most effective strategies for cancer treatment.

There is a marked increase in the expression of midkine by certain cancer cells, even at very early stages. Preclinical data shows that certain cancer cells lose their ability to grow and form tumours in the absence of midkine. Consequently, inhibiting midkine to prevent cancer growth and metastasis presents a highly targeted and potentially valid cancer treatment strategy.

In preclinical models of solid tumors growth has been significantly reduced or prevented altogether when midkine expression is halted using antisense or RNAi technology. The same observed when midkine is inhibited using anti-midkine antibodies. The proprietary monoclonal antibodies, RNAi technology and antisense oligonucleotides within the Midkine Intellectual Property Portfolio will be further developed, most likely through alliances and collaborations with suitable partners, for the treatment of solid tumors.

**Figure 6 Midkine antisense oligonucleotides in mouse CMT-93 cells**

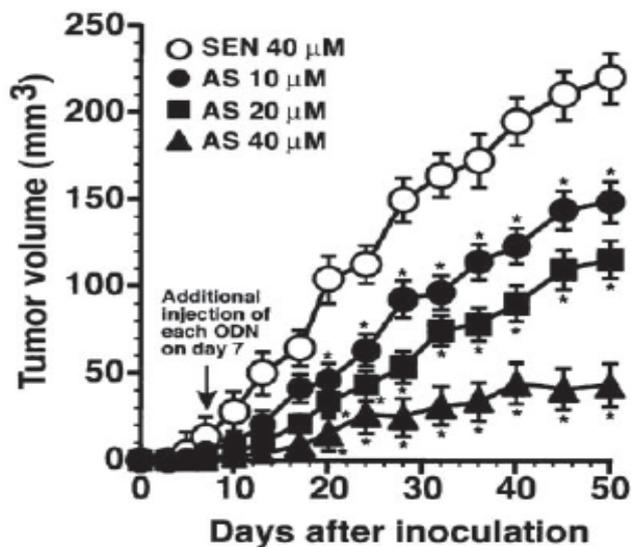


Midkine antisense oligonucleotides were introduced to mouse colorectal cancer cells (CMT-93) in vitro, reducing their ability to grow (●AS). When Midkine is added back to cells they regained their ability to grow (▲AS + MK).

<sup>3</sup> Herceptin sales alone represent around US\$4 billion annually.

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Figure 7 Midkine antisense oligonucleotides in a mouse model of colorectal cancer at various concentrations



Midkine antisense oligonucleotides were administered to mice (n=24) with colorectal cancer at day 1, 7, 21, 35 and 49. The treated mice had reduced tumour volume compared with the control. Increasing doses of antisense DNA resulted in corresponding reduction in tumour volumes. The effect was observed over a 50 day period.

### 2.3 Anti-midkine treatment for multiple sclerosis

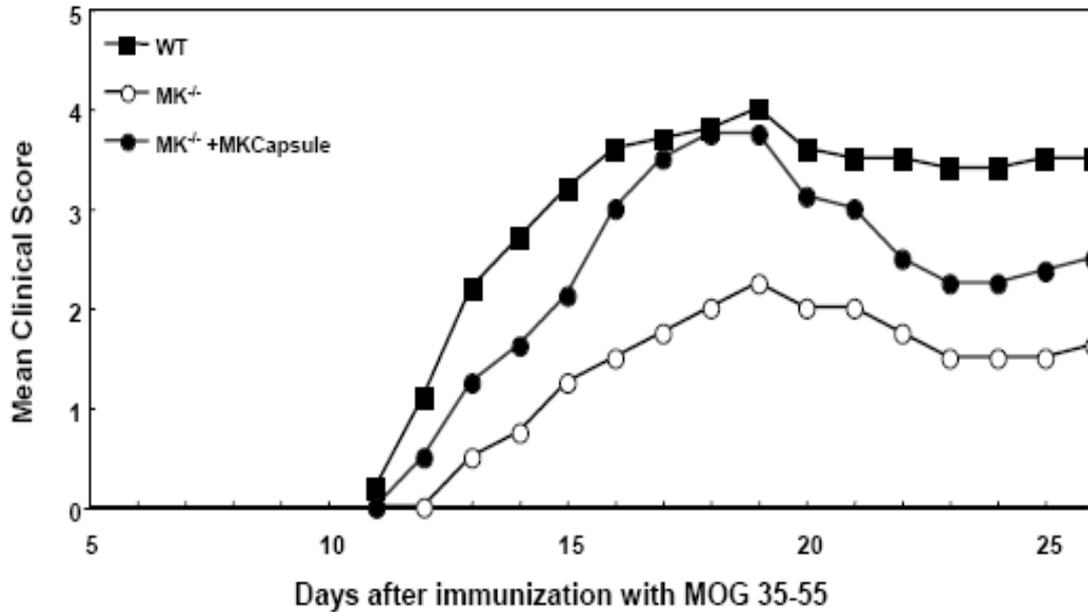
Multiple sclerosis is an autoimmune disease where the immune system attacks the protective myelin sheath of nerve cells and prevents them from conducting nerve impulses. An estimated three million people suffer from multiple sclerosis worldwide with almost one third of them not responding to current treatments.

While several disease modifying agents are available for the treatment of MS these only aim to slow progression of physical disability and reduce the number of relapses. In the absence of a cure there is clearly a need for more effective treatments which not only slow disease progression but could halt it altogether. Currently available therapeutic products collectively generated sales of US\$4.9 billion in 2006.

Midkine has a prominent role in the development of multiple sclerosis. This has been demonstrated by a mouse model of multiple sclerosis where Experimental Autoimmune Encephalomyelitis (EAE) was induced in mice by immunization with MOG35-55 (Figure 8). KO-MK mice (mice without midkine genes) did not develop severe symptoms of EAE, while mice with midkine genes not only developed severe EAE but they had a more rapid onset of the disease. Consequently, inhibition of midkine may provide an effective therapeutic strategy for multiple sclerosis.

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Figure 8 KO-MK mice in experimental autoimmune encephalomyelitis (EAE) show delay in the onset of EAE and a reduction in disease severity after immunisation with MOG35-55.



## 2.4 Anti-midkine treatment in other diseases

### Rheumatoid arthritis

Current treatments for Rheumatoid Arthritis (RA) include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, visco-supplements, anti-TNF, anti-IL-1 and anti-IL-2 treatments. In 2006 annual sales of these prescription drugs for the treatment of RA reached US\$16 billion. Preclinical research on a mouse model of rheumatoid arthritis demonstrated that 90% of those mice without midkine genes did not develop the disease. In comparison only 14% of the mice with midkine genes remained disease-free after inducing Rheumatoid Arthritis.

Table 2 Differences in the frequency of antibody induced arthritis between wild-type (WT) mice and mice deficient in the midkine (MK -/-) gene

| Mice                 | No of mice     |                   | Incidence % |
|----------------------|----------------|-------------------|-------------|
|                      | With arthritis | Without arthritis |             |
| WT                   | 6              | 1                 | 86%         |
| Mdk -/- No treatment | 1              | 9                 | 10%         |
| Mdk -/- HAS pump     | 3              | 8                 | 27%         |
| Mdk -/- MK pump      | 9              | 3                 | 75%         |

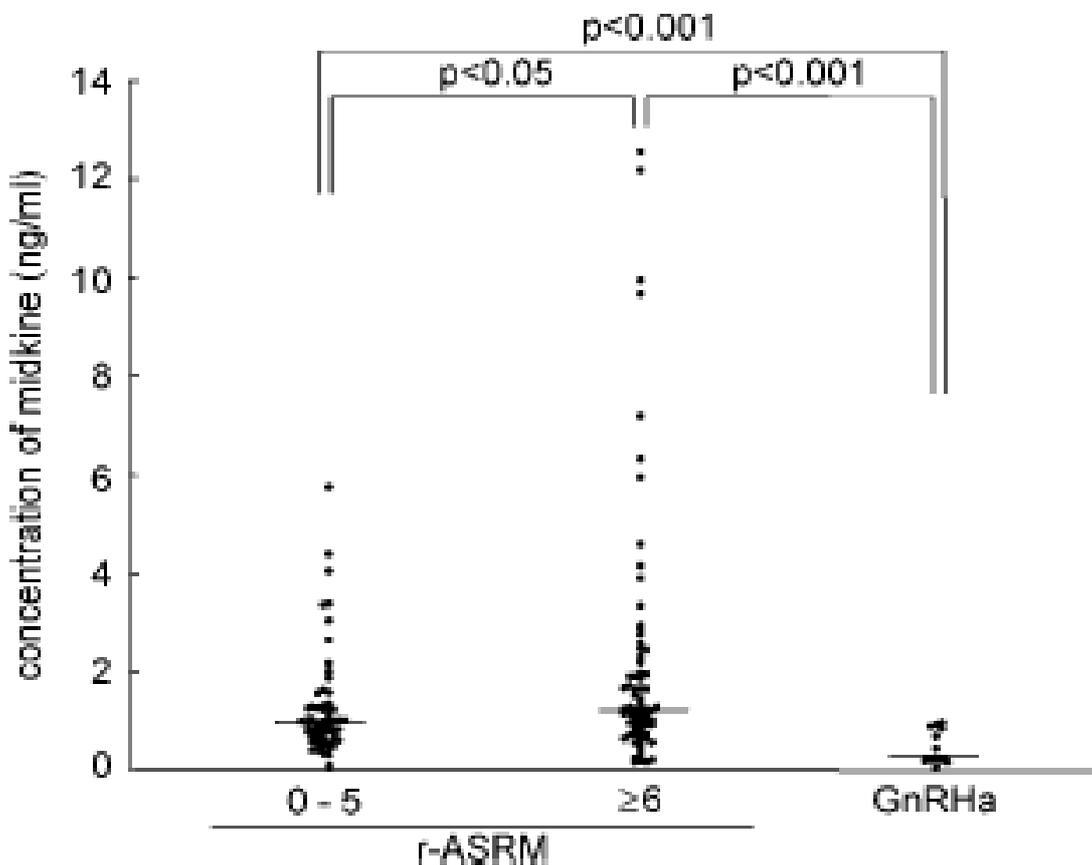
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## Endometriosis

At least 89 million women suffer from endometriosis worldwide. It is managed by pain medication such as NSAIDs, hormonal therapy such as gonadotrophin releasing hormone GnRH and surgery. The cost of pharmaceutical treatments alone is predicted to reach US\$2.2 billion by 2014.

Preclinical data to date suggest that midkine is involved in the development of endometriosis by promoting the growth of endometrial cells.

**Figure 9** Midkine concentrations in the peritoneal fluid of women with minimal endometriosis (r-ASRM score 0-5, n= 58), women with advanced endometriosis (r-ASRM score >6, n= 69) and women treated with GnRH agonist (n=12).



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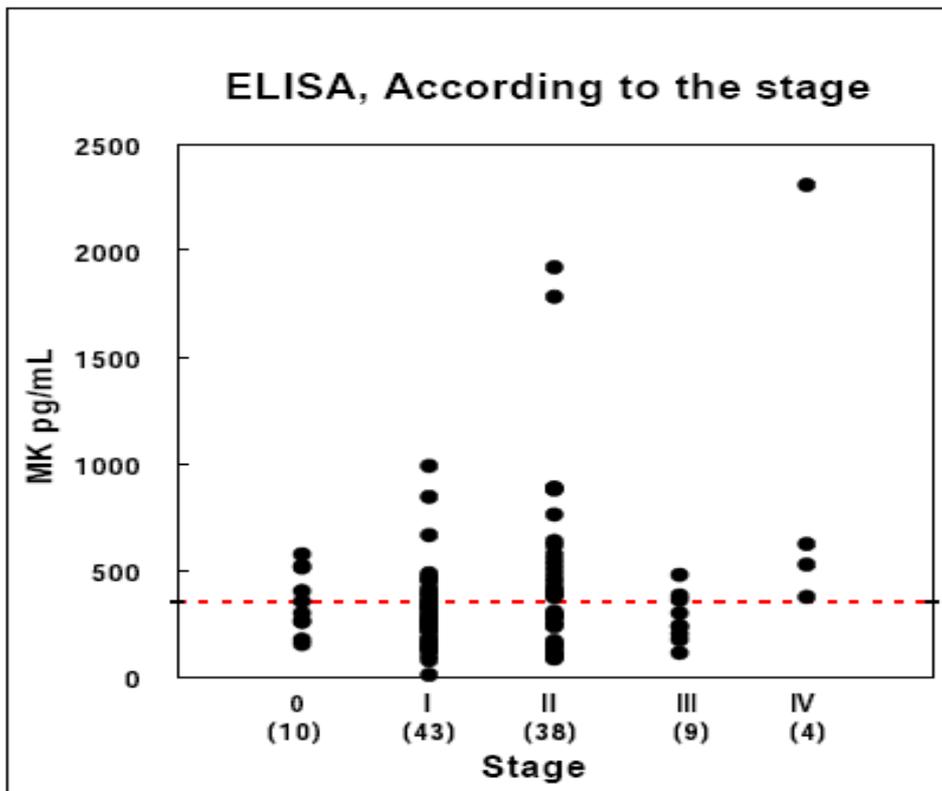
# 1. Midkine Diagnostics

Midkine based diagnostic blood tests have been successfully developed for early detection of cancer, and diagnosis of Sjogren's syndrome, Rheumatoid Arthritis and Alzheimer's disease. Using an Enzyme-linked Immunosorbent Assay (ELISA) midkine can be detected at low levels in the blood of healthy individuals (< 300 pg/ml) and is found at higher levels in people with tumour development, autoimmune and inflammatory disease (> 300 pg/ml). The ELISA tests are currently sold to the research market in Japan and collaborations will be pursued for extending the technology and commercialising it globally.

## 2.5 Early detection of cancer

High levels of midkine can be detected from early onset of cancer using ELISA (Figure 10). This is particularly important as early detection often means improved prognosis for patients.

Figure 10 Detection of breast cancer at various stages of progression



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Figure 11 Detection of midkine compared to other breast cancer biomarkers

| Breast cancer Stage | Other Biomarkers** |        |     | Midkine* |
|---------------------|--------------------|--------|-----|----------|
|                     | CA15-3             | BCA225 | CEA |          |
| 0                   | 0%                 | 0%     | 0%  | 45.5%    |
| I                   | 4%                 | 8%     | 6%  | 27.9%    |
| IIA                 | 8%                 | 22%    | 11% | 50.0%    |
| IIB                 |                    |        |     |          |
| IIIA                | 19%                | 39%    | 18% | 33.3%    |
| IIIB                |                    |        |     |          |
| IV                  | 38%                | 100%   | 56% | 100%     |

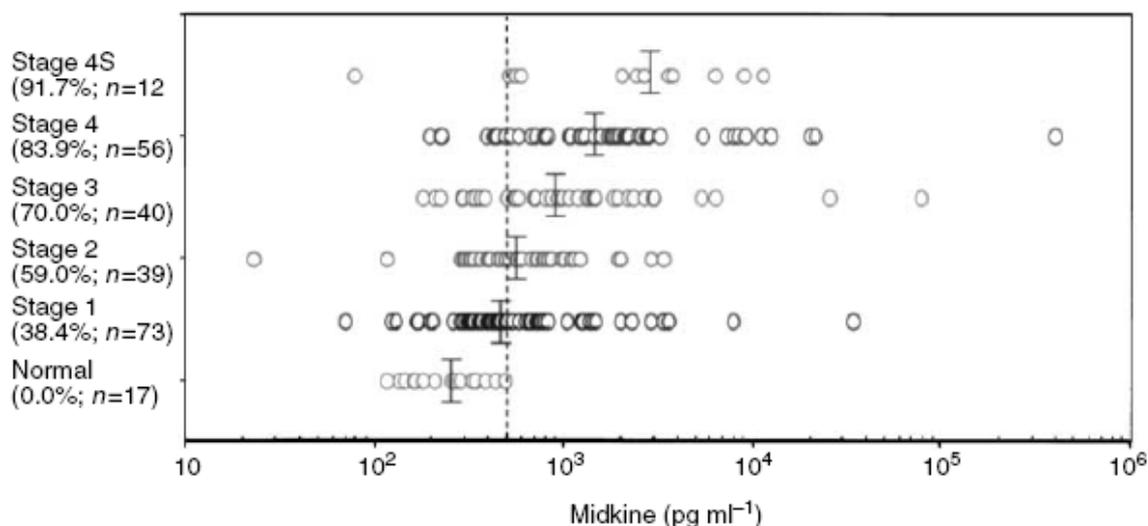
Source:\*Cell Signals, \*\*The Journal of The Japan Medical Association 2004

Midkine can be found in early stages of cancer development when other established cancer biomarkers are not detected (Figure 11).

## 2.6 Neuroblastoma screening for children

About one quarter of cancers in the first year of life are neuroblastomas. Children are routinely screened for neuroblastoma in Japan, Germany and Canada during health checks. Existing markers make it difficult to predict whether the condition is malignant requiring surgery or benign and self-resolving. Midkine levels correlate positively with the presence of early stage malignant neuroblastoma and therefore could become a screening method for this important early childhood condition.

Figure 12 Elevated levels of blood midkine correlate with poor prognosis in human neuroblastomas.



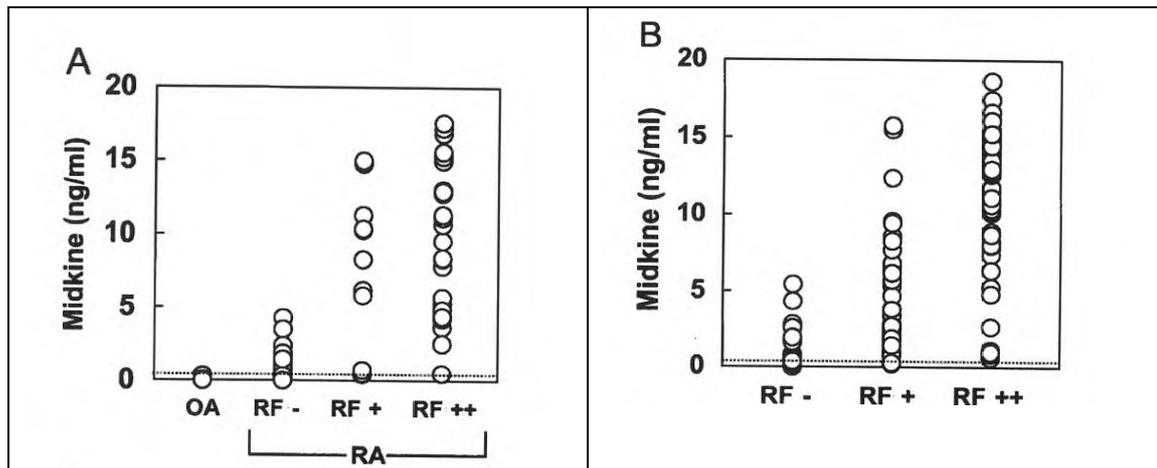
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## 2.7 Rheumatoid arthritis diagnosis

Midkine is a key molecule in the development of Rheumatoid Arthritis. Rheumatoid factor and anti-CCP antibodies are commonly found in the blood of people with the condition. High levels of midkine can also be detected in the synovial fluid of people with RA, assisting in the diagnosis of the condition.

**Figure 13 A** Increased levels of midkine detected in patients with rheumatoid arthritis (RA) in synovial fluid of patients with RA (n=55) or osteoarthritis (n=18)

**B** Levels of midkine increase with worsening rheumatoid arthritis



## 4. Summary

The Midkine Intellectual Property is a very rich portfolio of therapeutic and diagnostic technologies. A few of the potential applications for midkine, and for the proprietary anti-midkine antibodies and nucleotides, have been introduced in the previous pages. In addition, a large body of evidence in support of other patented therapeutic and diagnostic applications will also be assessed and included in the strategic planning process. The planning will take place immediately following the settlement of the transaction and is expected to result in a strong strategic program to deliver optimum value to Shareholders of MTY from the Midkine Intellectual Property Portfolio.

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# MEDICALTHERAPIES

## IMPORTANT DATES

**14 June 2008**

Due date for receipt of Proxy Forms

**16 June 2008**

EGM

**20 June 2008**

Expected Settlement Date for the Midkine Transaction

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