# Cellmid Limited

EGM Presentation

30 September 2011

CELLMID

# Disclaimer

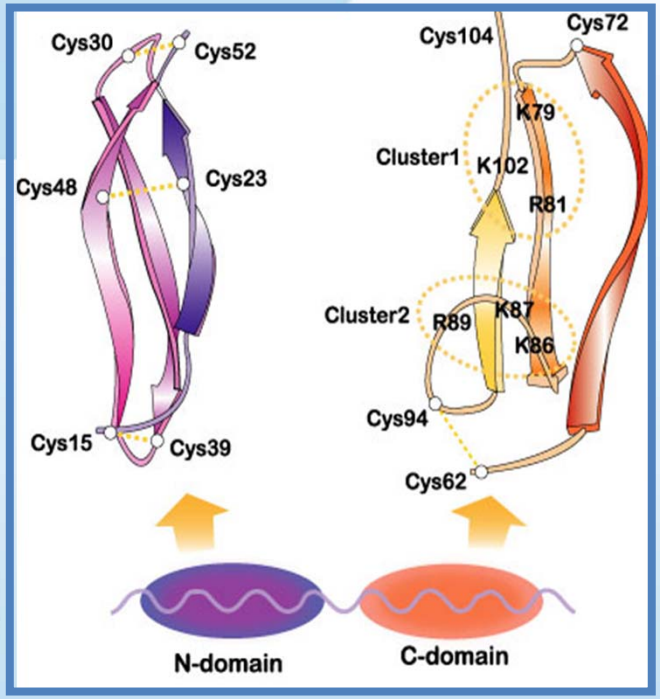
- This presentation includes forward-looking statements that are subject to risks and uncertainties. Such statements involve known and unknown risks and important factors that may cause the actual results, performance or achievements of Cellmid to be materially different from the statements in this presentation.

- Actual results could differ materially depending on factors such as the availability of resources, the results of clinical studies, the timing and effects of regulatory actions, the strength of competition and the effectiveness of the Company's patent protection.

# Cellmid Limited

- Australian biotechnology company, based in Sydney
- Cellmid owns a novel therapeutic and diagnostic target, midkine (MK), with 21 patent families corresponding to 12+ product lines
- Key product lines:
  - **Therapeutic:** Anti-midkine antibodies for the treatment of acute and chronic inflammatory conditions in preclinical development
  - **Therapeutic:** Midkine protein for the treatment of heart attack , stroke and chronic ischemia related diseases in preclinical development
  - **Diagnostic**: Cancer marker for the early diagnosis, prognosis and disease management of most cancers (licensed lung cancer diagnostic in 2009 to Celera)
  - **Cosmeceutical**: Market ready hair growth and hair health related products
- Key near term milestones:
  - **Humanisation** of the first ever anti-MK antibody (human drug) - 4Q2011
  - Complete **CE marking** of MK ELISA – 4Q2011
  - Commence **phase I trial** for anti-MK antibody - 4Q2012

# Midkine




- Embryonic growth factor, prominent in embryogenesis but largely undetectable in adults
- Small protein, 13kD, 121 amino acids with two domains
- Acts by
  - Inhibiting apoptosis
  - Facilitating cell migration
  - Modulating angiogenesis
  - Promoting cell growth
- Has an important role in onset of inflammatory diseases, cancer and in preservation and repair of injured tissue

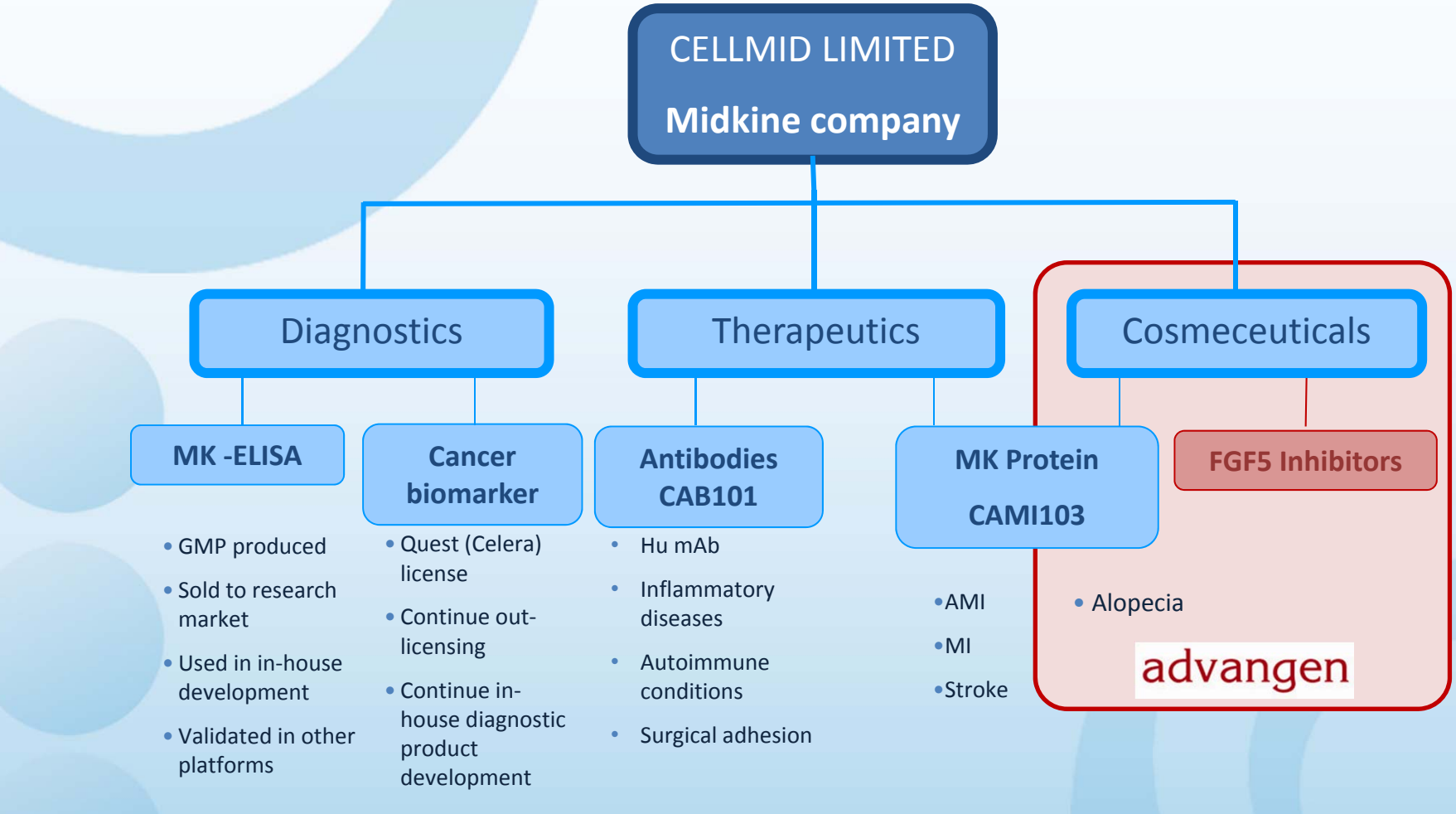
# Midkine portfolio has solid scientific foundations

- ~550 peer-reviewed publications, 250+ by Cellmid's inventors
- Many publications in top-line journals, covering all facets of MK biology
  - Gene, protein, structure, function, receptors
  - Human disease expression (tissue, blood, cancer, autoimmune, inflammation)
  - In vivo disease models, gene knockout and knockdown
  - Therapeutic intervention in models (RNAi, aptamers)

**Ten key papers from the last ten years:**


1. Fukui et al. (2008). "Therapeutic effect of midkine on cardiac remodeling in infarcted rat hearts." Ann Thorac Surg **85**(2): 562-570.
2. Hobo et al. (2009). "The growth factor midkine regulates the renin-angiotensin system in mice." J Clin Invest **119**(6): 1616-1625.
3. Horiba et al. (2006). "Midkine plays a protective role against cardiac ischemia/reperfusion injury through a reduction of apoptotic reaction." Circulation **114**(16): 1713-1720.
4. Ibusuki et al. (2009). "Midkine in plasma as a novel breast cancer marker." Cancer Sci **100**(9): 1735-1739.
5. Ishiguro et al. (2011). "A single intracoronary injection of midkine reduces ischemia/reperfusion injury in swine hearts: a novel therapeutic approach for acute coronary syndrome." Frontiers in Physiology **2**.
6. Kato et al. (2011). "Growth factor Midkine is involved in the pathogenesis of renal injury induced by protein overload containing endotoxin." Clinical and Experimental Nephrology: 1-9.
7. Sato et al. (2001). "Midkine is involved in neutrophil infiltration into the tubulointerstitium in ischemic renal injury." J Immunol **167**(6): 3463-3469.
8. Sato et al. (2005). "Midkine antisense oligodeoxyribonucleotide inhibits renal damage induced by ischemic reperfusion." Kidney Int **67**(4): 1330-1339.
9. Sumida et al. (2010). "Midkine gene transfer after myocardial infarction in rats prevents remodelling and ameliorates cardiac dysfunction." Cardiovasc Res **86**(1): 113-121.
10. Wang et al. (2008). "Inhibition of midkine alleviates experimental autoimmune encephalomyelitis through the expansion of regulatory T cell population." Proc Natl Acad Sci U S A **105**(10): 3915-3920.

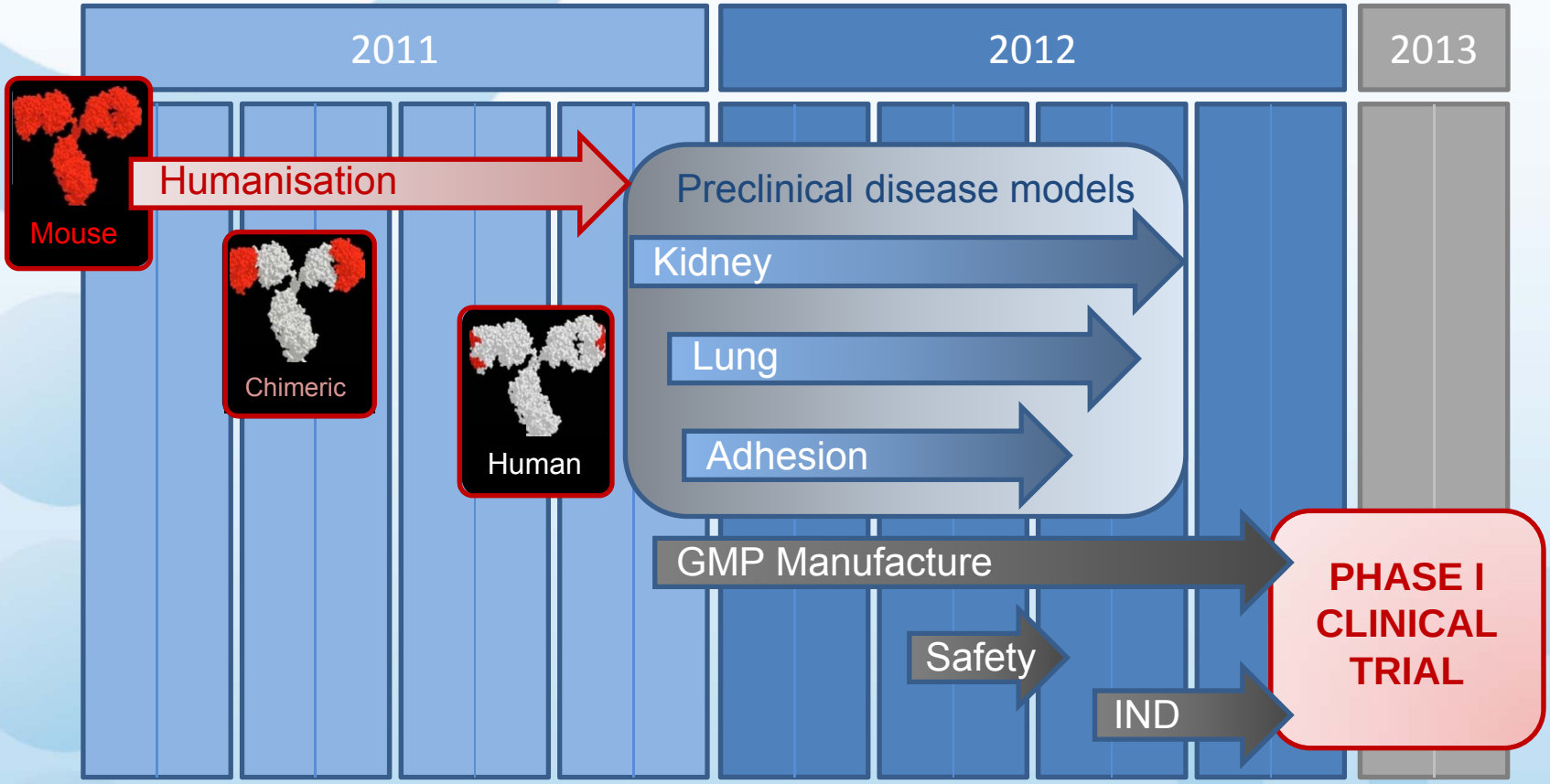
# Cellmid programs



# Recent highlights

- November 2010 Midkine ELISA launched (independently validated)
- November 2010 Inaugural midkine conference with 50 scientists attending
- December 2010 Launch of Advangen range of hair growth products
- April 2011 Completion of proof of concept study for heart attack
- April 2011 Signed a collaboration with Antitope to humanise lead MK antibody
- May 2011 Milestone report from Celera lung cancer diagnostic license
- August 2011 Completed GMP manufacture of midkine ELISA

# Antibody program 2011-2012



# MK antibody: Rationale and clinical strategy

- Inflammatory conditions where neutrophil/macrophage infiltration drives disease
  - Strongest mechanism of action evidence for anti-MK agents (literature, in-house)
- Lead indications:
  1. Kidney inflammation (AKI and CKD)
  2. Lung inflammation (COPD)
  3. Surgical adhesion
- Large markets with no/unsatisfactory current treatment options:
  - Clinically significant diseases
  - Significant current economic burden – early reimbursement
- Speed to market:
  - Parallel pre-clinical in vivo testing to move lead indication rapidly to phase I trial
- Strong intellectual property protection with preference to blocking IP

# Kidney diseases represent significant economic burden

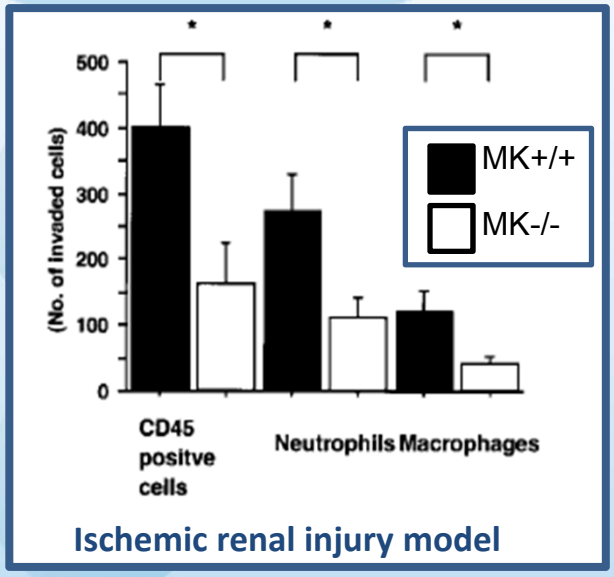
- **Acute kidney injury (AKI)**
  - 3-7% of hospital admissions, 25-30% of ICU patients[1]
  - US: ~600,000 new cases per year[2]
  - Increased mortality, complicates hospital outcomes (longer stay, ICU care, dialysis)
  - Estimated >20% AKI patients progress to CKD
  - Limited drug interventions available currently
- **Chronic kidney disease (CKD)**
  - 2009 global market $13.3 billion (2016 forecast: $19.8 billion)[3]
  - US: 26 million CKD patients, another 20 million at risk
  - Progressive disease with costs rising dramatically with advancement toward kidney failure (dialysis, transplantation)
  - Long term drugs for management only: blood pressure regulation
- **MK Antibody- many opportunities in KD**
  - **AKI**- reduce hospital stay, prevent progression to CKD
  - **CKD**-prevent or delay progression to costly end stages of disease
  - Likely safety profile very good , allowing long term multi-treatment



1 *Brenner and Rector's The Kidney*. Philadelphia: Saunders (2007)
2 Chawla 2011, *Kidney International* (2011) **79,** 1361–1369
3 GlobalData Report (2010*) Chronic Kidney Disease - Drug Pipeline Analysis and Market Forecasts to 2016*

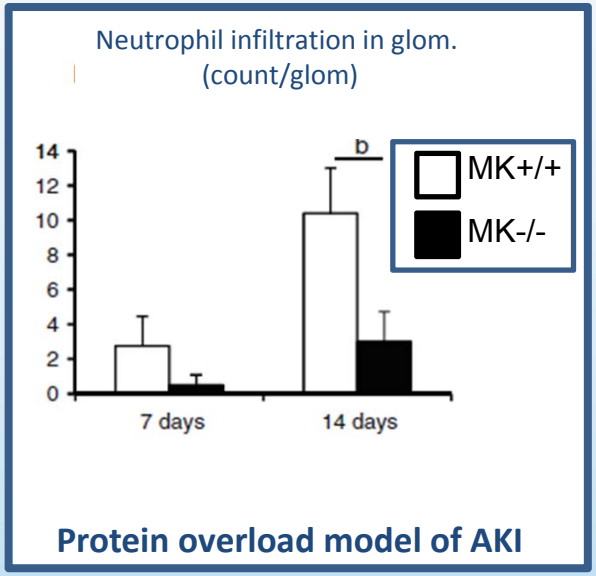
# Midkine elicits inflammatory kidney disease

- MK recruits neutrophils and macrophages to kidney
- MK upstream of TGF-β and MIP-2



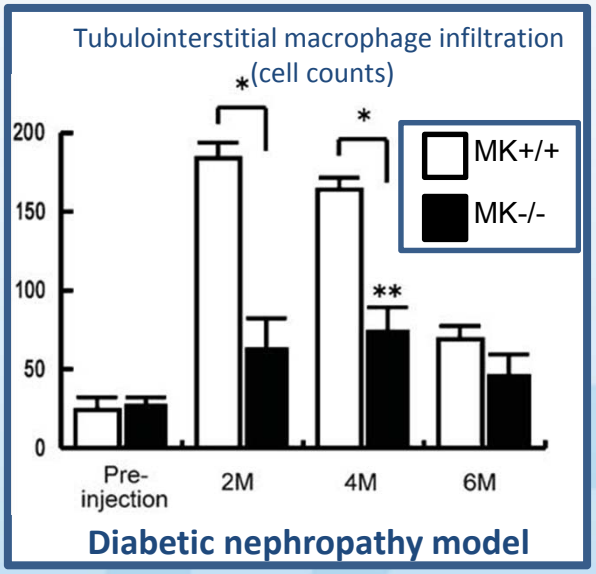

**Ischemic renal injury model**

Sato *et al* 2001




**Protein overload model of AKI**

Kato *et al* 2011

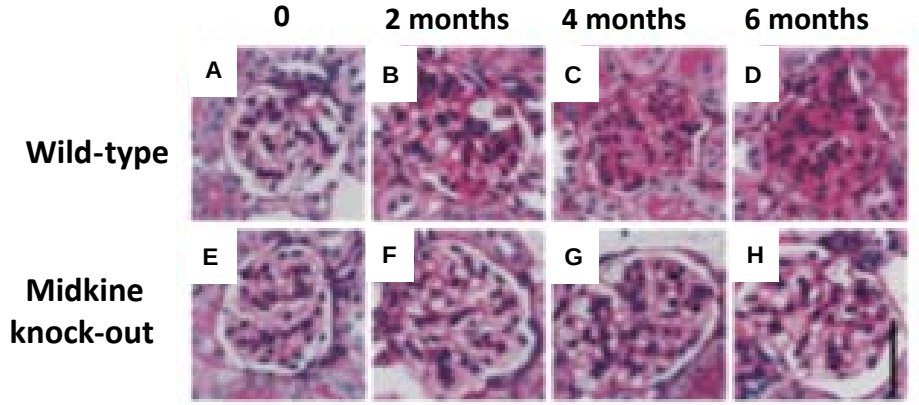



**Diabetic nephropathy model**

Kosugi *et al* 2007

# Midkine in diabetic nephropathy

- Nodular lesions occur in $Mdk^{+/+}$ mice only
- Kidney function (uPr, BUN) preserved in $Mdk^{-/-}$

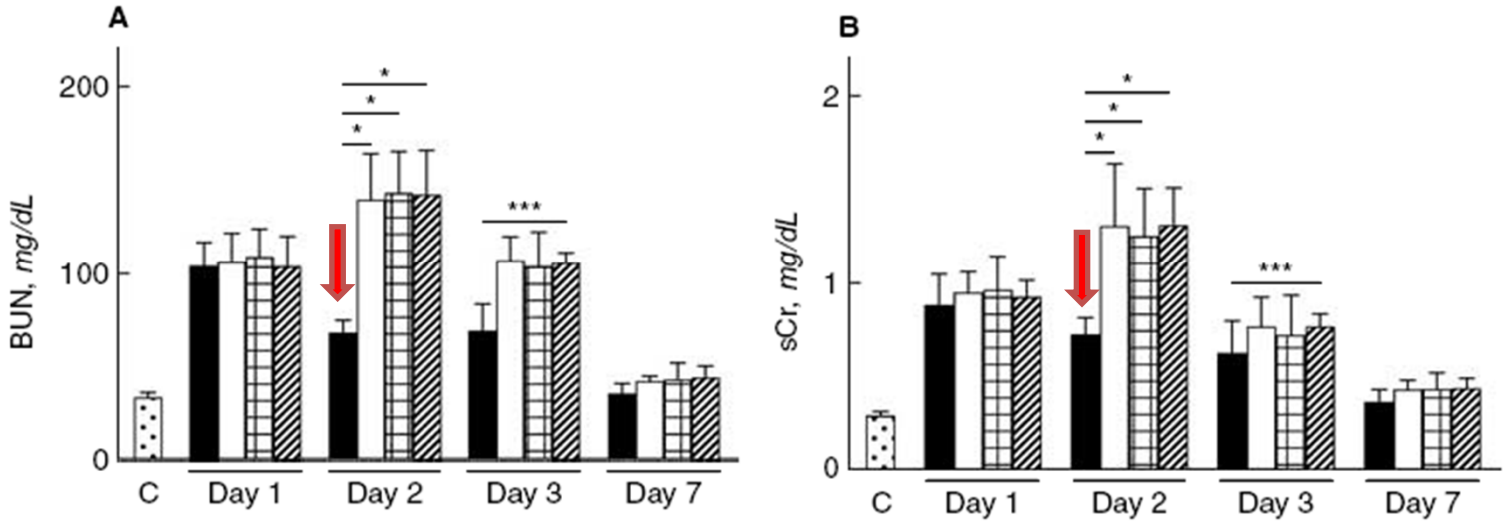



**MK is a key molecule in the pathogenesis of diabetic nephropathy.** Nephropathy was induced using Streptozotocin in $Mdk^{+/+}$ and Mdk knockout mice and glomerular damage was monitored for 6 months. Diabetic nodular lesions developed in $Mdk^{+/+}$ mice (A-D) but not in $Mdk^{-/-}$ mice (E-H).

Kosugi *et al* 2006

# MK antisense reduces kidney damage

- Inflammatory renal damage reduced by MK antisense (AS)
- Kidney function preserved
- Therapeutic intervention- AS given *after* I/R event




**Midkine antisense (MK AS) treatment reduces kidney damage from I/R injury**. One day after I/R injury mice were administered MK AS (black bars), MK sense (white), scrambled (checked) or saline only (diagonal hatching). Kidney damage was assessed by blood urea nitrogen (A) and serum creatinine (B) over 7 days. *P<0.01; ***P<0.005 (*n*=12)

Sato *et al* 2006

# Chronic Obstructive Pulmonary Disease (COPD)

- ~12 million people were identified with COPD in 2000 and a further 12 million were predicted to have undiagnosed COPD[1]
- COPD is the physiological finding of non-reversible pulmonary function impairments, it covers a constellation of conditions including chronic bronchitis and emphysema
- In 2000, COPD was responsible for[1]:
  - 8 million physician office and hospital outpatient visits
  - 1.5 million emergency department visits
  - 726,000 hospitalizations and
  - 119,000 deaths
- The economic burden of COPD in the U.S. in 2007 was **$42.6 billion** in health care costs and lost productivity[2]
- Many of the current treatments for COPD are effective at reducing the symptoms of the disease, however, there remains an urgent need for new treatments that impact long-term management



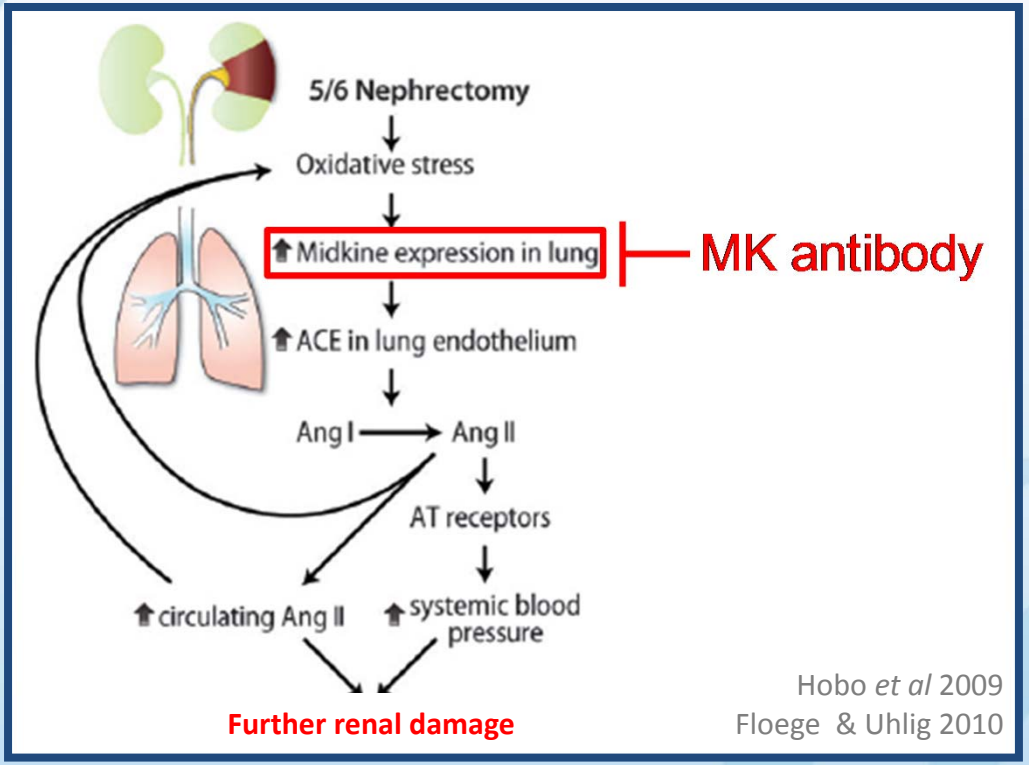
1 Mannino D M, Homa D M, Akinbami LJ, et al. Chronic Obstructive Pulmonary Disease Surveillance—United States, 1971-2000. *M M W R.* August 2, 2002;51(SS06):1-16.
2 Thom, T. (2007) Morbidity and mortality: 2007 Chart book on cardiovascular, lung and blood disease. National Institutes of Health. Access at: http://www.nhlbi.nih.gov/resources/docs/07a-chtbk.pdf

# Midkine's role in lung inflammation

- COPD in conjunction with esophageal carcinoma correlates to high serum MK
- Mk causes inflammatory cell infiltration in the lungs
- MK causes pulmonary vascular remodeling during hypoxia
- Hypertension induced by lung MK expression
- Kidney-lung feedback (renal damage leading to lung inflammation)

# MK upregulates ACE in acute kidney injury

- **WT vs Mdk$^{-/-}$ after 5/6 nephrectomy**




Hobo *et al* 2009
Floege & Uhlig 2010

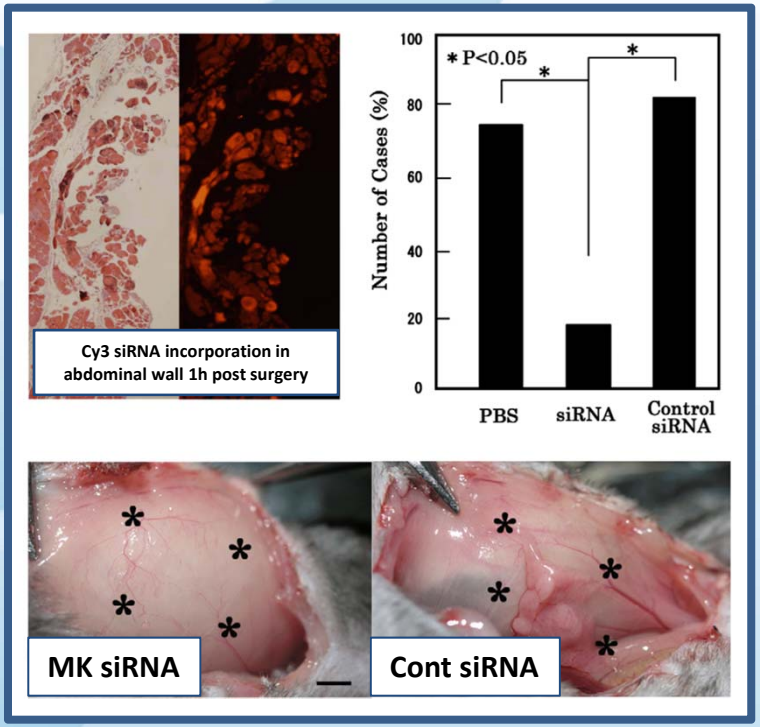
# Surgical adhesion

- Adhesion: build up of internal scarring which results in connecting different organs following surgery (causes severe pain and infertility)
- Adhesions occur in **over 95%** of abdominal operations[1]
- Adhesions account for 6% of all readmissions following surgery[1]
- Post-surgical anti-adhesion market is estimated at **$3 billion** in the US and $5 billion globally[2]
- **Currently no drugs** available for treatment
- Follow up surgery is used but ~85% of the time it results in more adhesions[3]
- Leading methods for prevention:
  - Genzyme: Seprafilm (temporary, bio-resorbable adhesion barrier)
  - J&J: Interceed (bio-absorbable barrier)
- Possibility: pre-condition patients with anti-MK antibody prior to/at surgery
  - Pre-treating increases chance of therapy working



1 Stanciu, D. and Menzies, D. (2007), The magnitude of adhesion-related problems. Colorectal Disease, 9: 35–38. doi: 10.1111/j.1463-1318.2007.01346.x
2 Cardiovascular Sciences (2011) Investor Relations = access at http://www.cvsciences.org/index-2.html
3 Parker, M. *et al* (2007), Adhesions and Colorectal Surgery – Call for Action. Colorectal Disease, 9: 66–72. doi: 10.1111/j.1463-1318.2007.01342.x

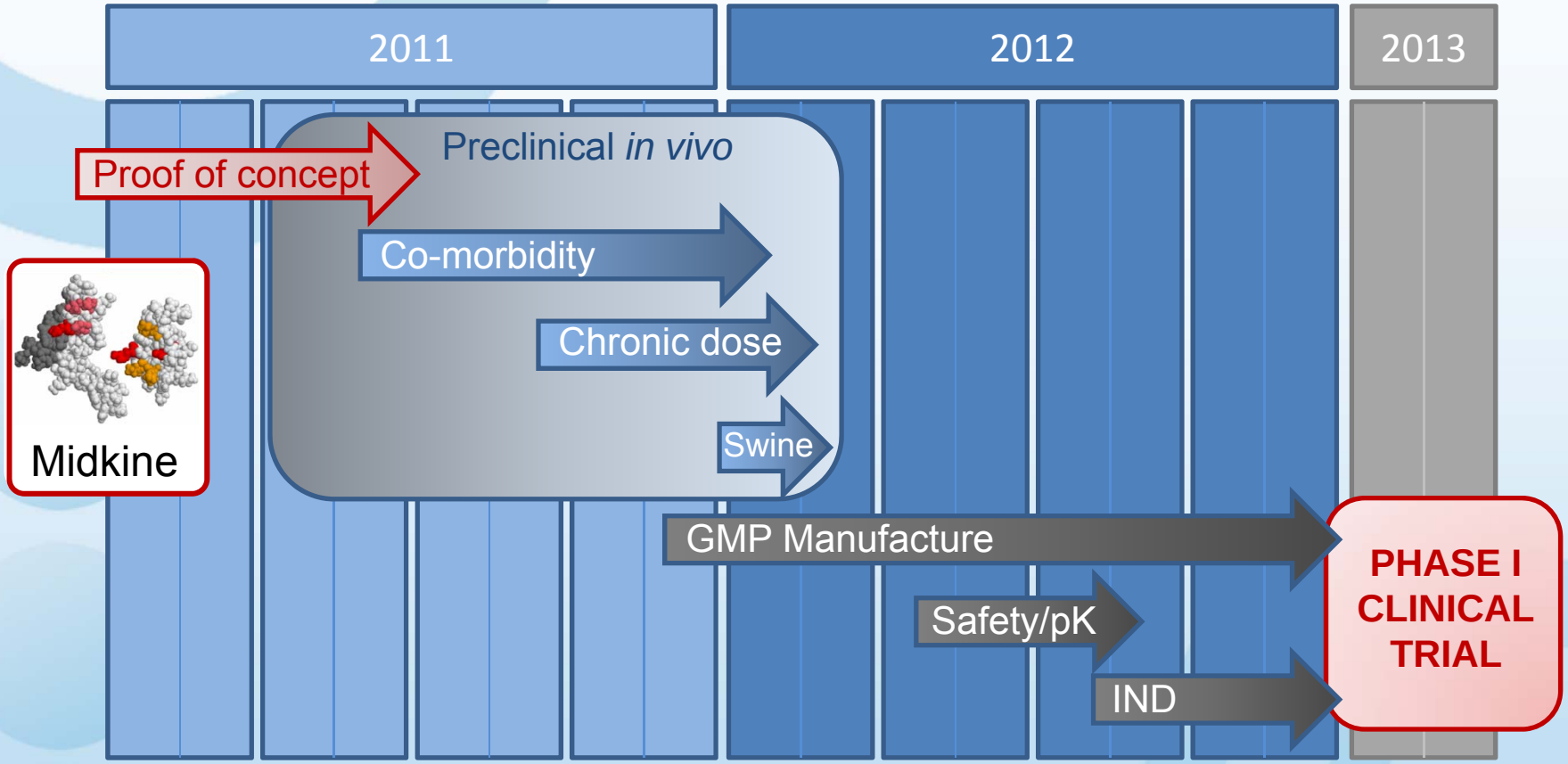
# Midkine in surgical adhesion




Inoh *et al* 2004

- Adhesions greatly reduced in MK -/- mice
- Inflammatory cell involvement (inflammatory cell migration triggers build up of collagen and connective tissue)
- siRNA administered intra-peritoneally after surgery reduces adhesions

# AMI program 2011-2012



# Myocardial Infarction (MI)

- In 2002, 12.6%of worldwide deaths were from ischemic heart disease[1]
- ~50% of deaths occur **within one hour** of an AMI outside a hospital[2]
- In the USA AMI costs **$31 billion** for inpatient hospital charges[3]
- Early intervention is imperative to reduce or prevent myocardial damage. There is a vast, currently unmet, need for new compounds that prevent heart failure by reducing the damage inflicted by heart attack.
- Possibility: An emergency dose of MK given to patients by coronary artery infusion via standard catheter as soon as possible after heart attack. MK may also be given in conjunction with current procedures such as clot-busting and stent technologies.
  - Reducing heart damage due to heart attack would make midkine one of the first in a new class of drugs and attractive to health insurers and providers worldwide.

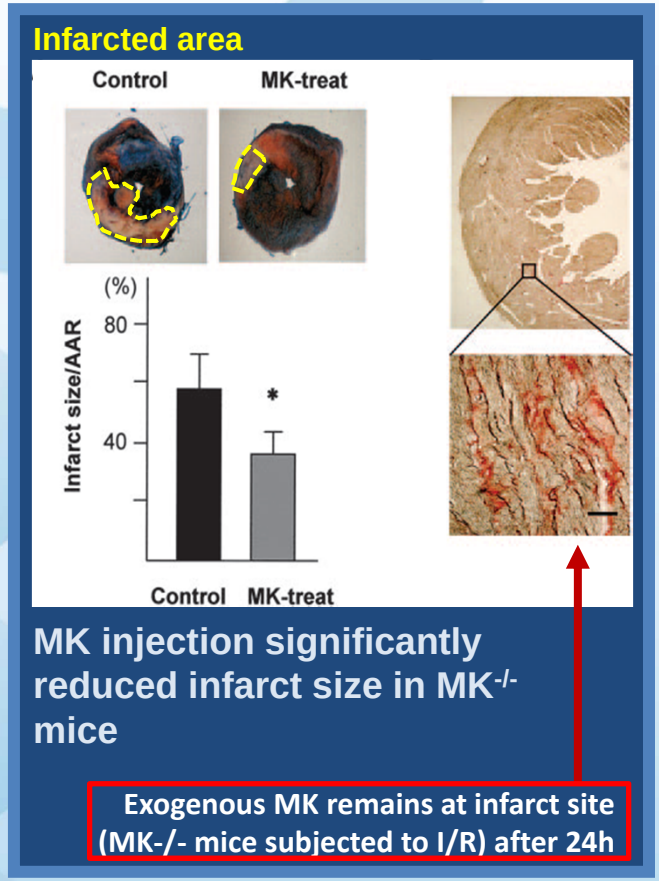


1 Robert Beaglehole, et al. (2004). The World Health Report 2004 – Changing History. World Health Organization. pp. 120–4. ISBN 92-4-156265-X. http://www.who.int/entity/whr/2004/en/report04_en.pdf.
2 National heart, lung and blood institute (2011) National Heart Attack Alert Program. Access at: http://www.nhlbi.nih.gov/about/nhaap/nhaap_pd.htm
3 Bruce B. Lerman, Craig T. Basson (2009). Topics in Arrhythmias and Ischemic Heart Disease. Demos Medical Publishing, pg 63

# Midkine therapy for MI: treatment for acute & chronic conditions

- Prevents heart muscle death in acute stage (AMI)
  - Reduces cardiomyocyte apoptosis
  - Decreases infarct area
  - Enhances immediate survival
- Reduces chronic heart problems in aftermath of MI
  - Prevents cardiac remodeling
  - Increases neo-vascularisation in the infarct
  - Improves long term survival

# MK therapy protects against cardiac ischemia/reperfusion

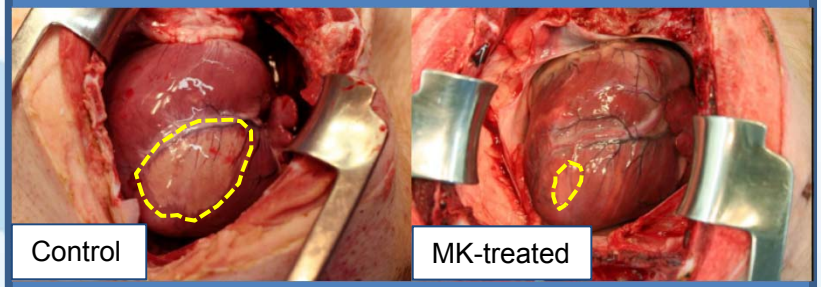



Horiba *et al* 2006

- Mouse model of myocardial injury after ischemia/reperfusion (I/R) related transient occlusion of coronary arteries
- Increased survival in untreated WT ($MK^{+/+}$) vs untreated MK KO ($MK^{-/-}$)mice
- MK expression increased in WT mice after I/R, decreased apoptosis in WT vs $MK^{-/-}$ mice
- 10μg/mL (20μL) MK injection (injected into peri-infarct area of LV) reduced infarct size in MK-/- mice

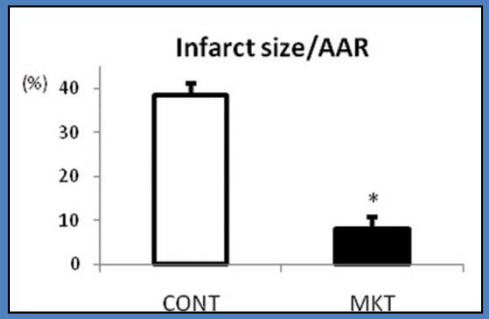
# MK reduced mortality in a large animal model

**Infarcted area**




Mortality rate after 24 hours:

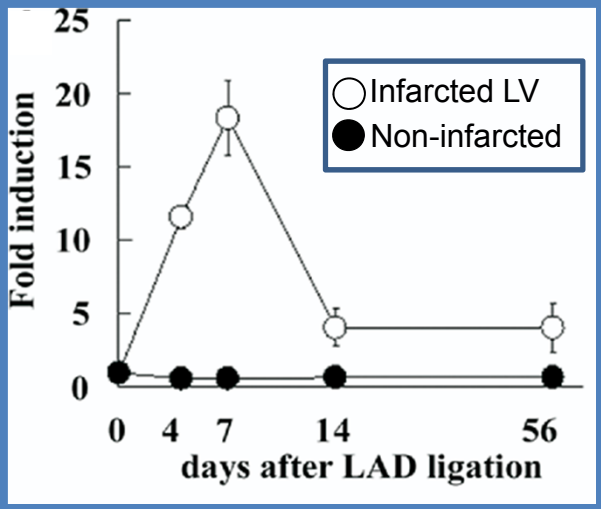
- Control: **4/12 (33.3%)**
- MK-treated: **1/9 (11.1%)**




Ishiguro *et al* 2011

- Porcine model of AMI - balloon placed distally to the first diagonal artery for 45 minutes
- Following ischemia 5µg/kg MK injected directly into the ischemic area upon reperfusion
- Single dose of MK **reduced mortality three-fold**
- Single dose of MK **reduced infarct area five-fold**

# Delayed and chronic MK therapy

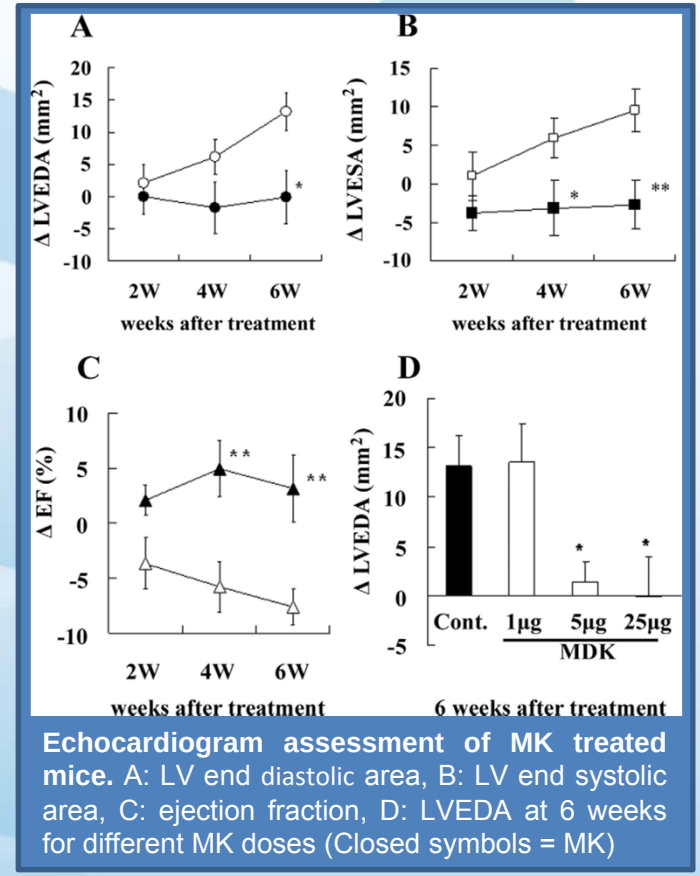



**Expression of MK mRNA in infarcted rat hearts peaks ~7 days after surgical occlusion**

Fukui *et al* 2008

- Single dose of MK delivered close to time of infarct
  - Reduced apoptosis
  - Reduced infarct size
  - Decreased mortality
  - Rat and swine studies
- What about longer term effects?
  - Delayed MK dosing in rat model
  - Chronic MK dosing in murine model

# Single, delayed MK dose saves heart function

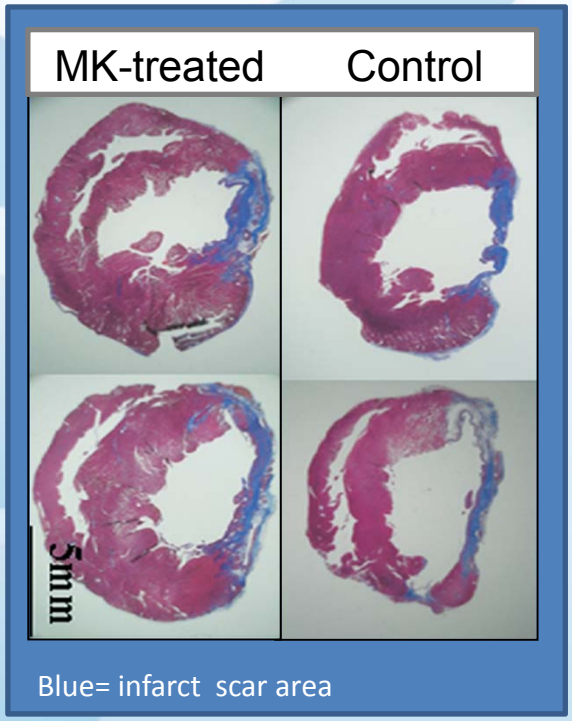



**Echocardiogram assessment of MK treated mice.** A: LV end diastolic area, B: LV end systolic area, C: ejection fraction, D: LVEDA at 6 weeks for different MK doses (Closed symbols = MK)

Fukui *et al* 2008

- Rat model- surgical MI followed by MK dose 2 weeks later
  - Direct injection to border zone myocardium of MK in collagen gel
- Cardiac function monitored up to 6 weeks post MI
- Morphometric analysis at 6 weeks post MI
- MK treatment **improved heart function**, **inhibited ventricular remodeling** and **increased vascular density**

# Single, delayed MK dose attenuates LV remodeling




Blue= infarct scar area

Fukui *et al* 2008

- Morphometric analysis 6 weeks post-MI (25μg MK)
  - **Smaller LV cavity** after MK treatment
  - **Thicker ventricular muscle** after MK treatment
  - **Thicker infarct scar** after MK treatment, but similar MI area in treated and control groups
- Delayed MK dosing does not reduce infarct area, but does attenuate LV remodeling

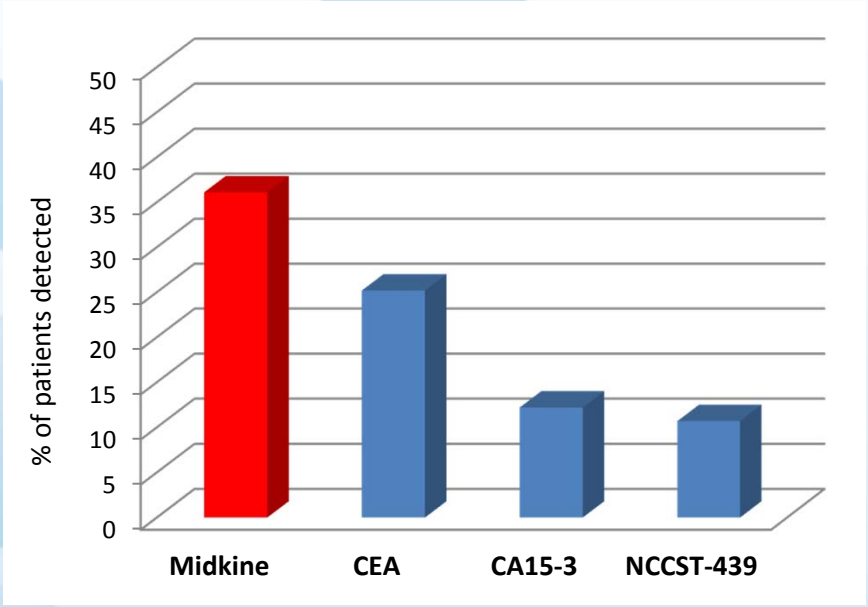
# MK as a cancer biomarker

- Cancer biomarker readily detected in serum/plasma
- Blood elevation of MK often precedes symptoms –early detection
- **Adds value in the full cancer management spectrum** (screening, diagnosis, prognosis, treatment monitoring, detecting recurrence)

MK is over-expressed in tissue and/or blood for at least 26 different cancers

| | Breast | Prostate | Ovarian | Cervical | Uterine | Lung (NSC) | Lung (SC) | Lung (brain mets) | Neuroblastoma | Glioblastoma | Medulloblastoma | Primative neurectodermal | Meninginoma | Neurofribromatosis type I | Gastric | GI stromal | Bladder | Colorectal | Duodenal | Oral squamous cell carcinoma | Osophageal SCC | Hepatocellular | Bile Duct | Pancreatic | Thyroid | Osteosarcoma |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Blood** | ✔ | | ✔ | | ✔ | ✔ | ✔ | ✔ | ✔ | | | | | ✔ | ✔ | ✔ | | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | |
| **Tissue** | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | | ✔ | ✔ | ✔ | ✔ | | ✔ | ✔ | ✔ | | ✔ | ✔ | ✔ |

# Breast cancer detection

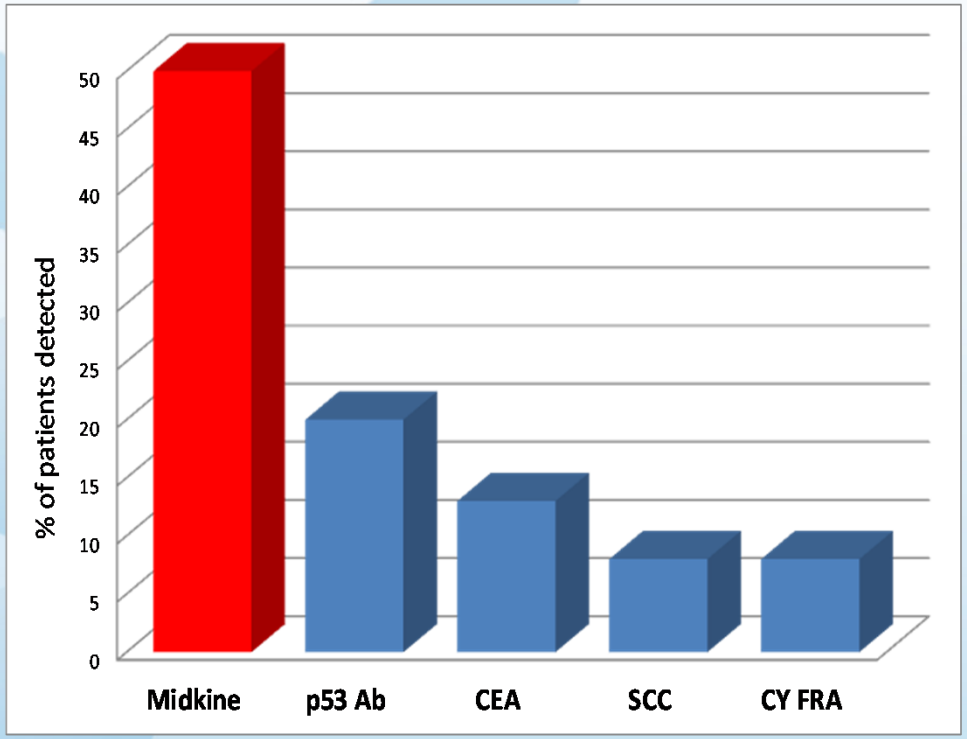



| Combination of markers | Detection rate |
|---|---|
| 1.CA15-3/CEA/NCCST-439 | 29.9% |
| 2.MK/CA15-3/CEA | 44.9% |
| 3.MK/CA15-3/NCCST-439 | 41.5% |
| 4.MK/CEA/NCCST-439 | 44.9% |

Ibusuki *et al* 2009

- MK out-performs other biomarkers in breast cancer detection
- Measuring serum midkine concentrations in breast cancer patients, either alone or in combination with conventional markers, significantly enhances disease detection (n=147)

# Early detection of esophageal cancer



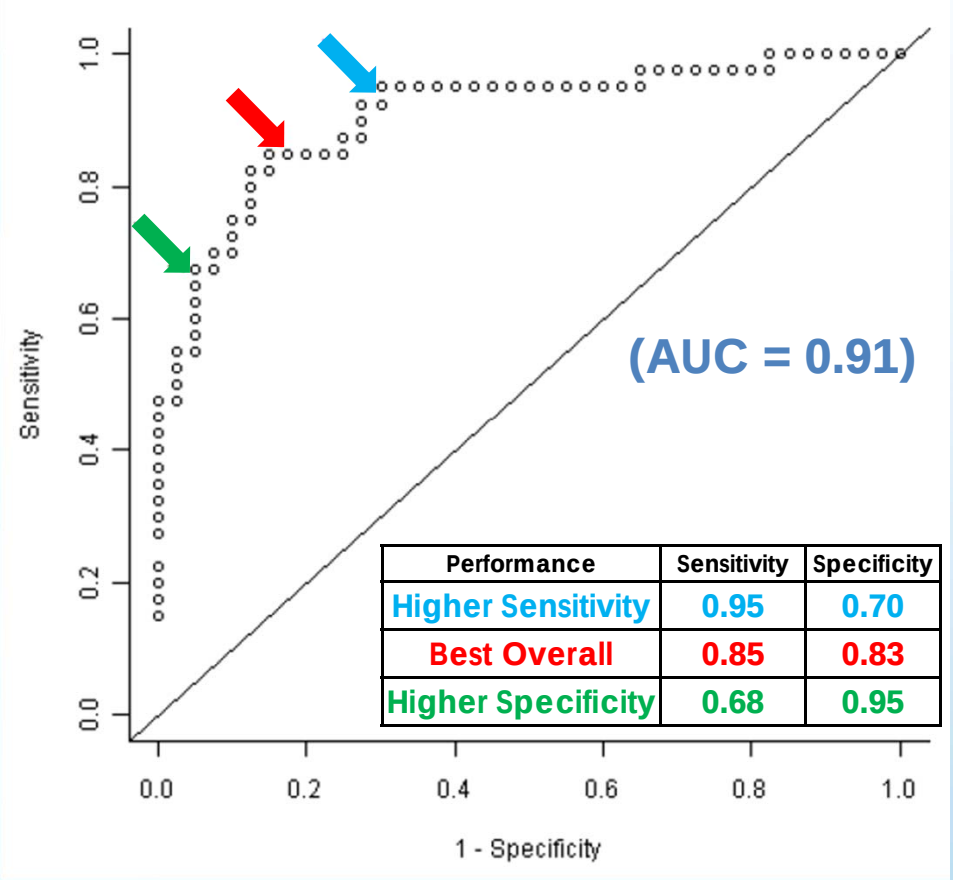

Using serum MK cut-off of >300pg/mL (mean normal serum MK conc. + 2 std. deviations)

Shimada *et al* 2003

- MK out-performs other biomarkers in stage 1 ESCC detection
- MK serum concentration in 60 Stage I superficial esophageal squamous cell carcinoma patients (ESCC) greatly enhances disease detection over conventional markers

# Early detection of lung cancer

SIX BIOMARKER PANEL FOR EARLY STAGE LUNG CANCER DETECTION

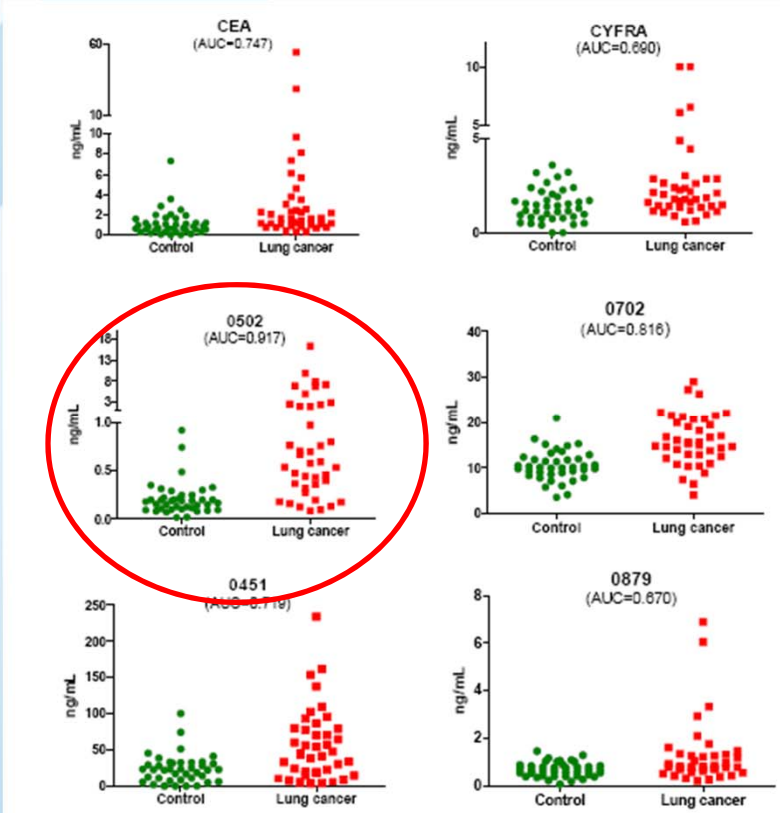



- **Celera (Quest) - Six biomarker lung cancer diagnostic test**
- 20% of all lung cancers are found in the 'never smoker' populations with non-specific lung complaints.
- ~85% of patients diagnosed with late stage disease with a 5 year survival rate of only 15% - There is a significant unmet need to detect early lung cancer with
- MK is the best performing of the six biomarkers on Celera's newly developed panel identifying malignant lung cancers in a 'never smoker' cohort
- A potential adjunctive tool to CT scanning which has a low specificity of around 75% and associated morbidity

This information was presented by Celera Corporation on 4 April 2011 at the 102nd Annual Meeting of the American Association of Cancer Research

# Early detection of lung cancer

- Performance of individual markers - never smoker study



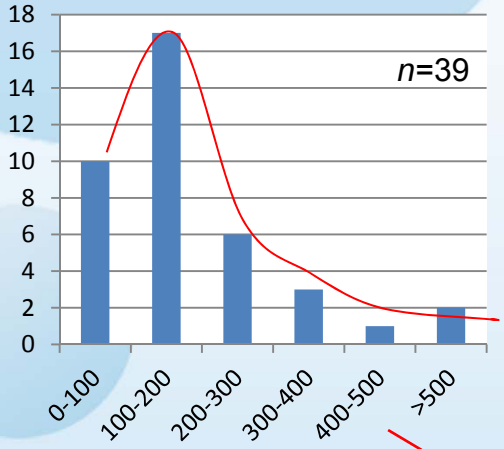

| | Never Smoker | | Smoker | |
|---|---|---|---|---|
| | AUC | P value | AUC | P value |
| CEA | 0.747 | 0.0001 | 0.664 | < 0.0001 |
| CYFRA | 0.690 | 0.0035 | 0.767 | < 0.0001 |
| 0502 | 0.917 | < 0.0001 | 0.669 | < 0.0001 |
| 0702 | 0.816 | < 0.0001 | 0.711 | < 0.0001 |
| 0451 | 0.719 | 0.0008 | 0.623 | 0.0002 |
| 0879 | 0.670 | 0.0090 | 0.730 | < 0.0001 |

- Comparison of individual markers in never smoker and smoker studies

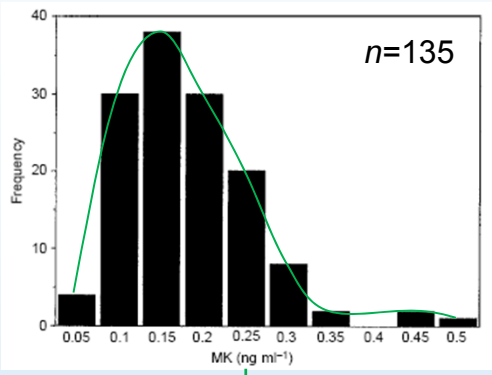
This information was presented by Celera Corporation on 4 April 2011 at the 102nd Annual Meeting of the American Association of Cancer Research

# MK detection footprint in different samples

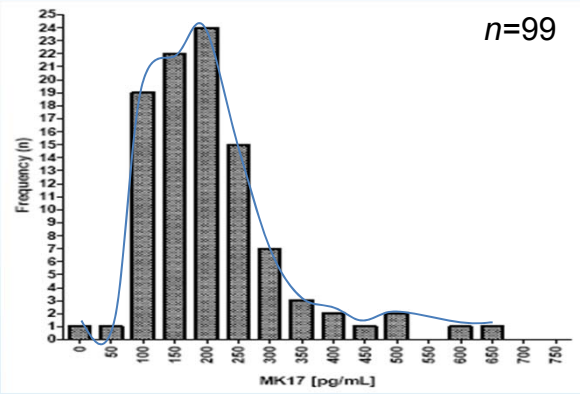
**Celera 0502**

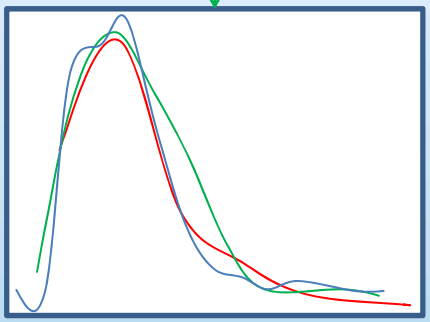



**Ikematsu 2000**




**BioGenes report 32491**



# Cellmid's upcoming milestones

## MK Antibody

- Humanisation of the first ever anti-MK antibody (human drug) - 4Q2011
- Complete preclinical testing on first indication– 2Q2012
- Commence phase I clinical trials- 4Q2012

## MK Protein

- Complete stages 4 and 5 of AMI pre-clinical trials in preparation for IND – 2Q2012
- Complete GMP manufacture of midkine - 1Q2013
- Commence phase I trial- 1Q2013

## MK Diagnostic

- Complete CE marking of MK ELISA – 4Q2011
- Complete CK3000 clinical trials (healthy reference values) - 4Q2011
- Complete stage 1 veterinary (canine) cancer diagnostic - 4Q2011
- Commence John Hunter Hospital cancer diagnostic trials – 4Q2011

# Investment highlights

- **Multiple revenue source – unique target**
  - Cancer **diagnostic** licenses to third parties
  - Cancer **diagnostic** in-house products
  - Antibody **therapeutics** (several inflammatory diseases with large potential markets)
  - Midkine protein **therapeutics** (AMI, MI and stroke)
  - **Cosmeceuticals** (Hair growth, hair health) – immediate revenue source
- **Reduced risk**
  - Diagnostic and therapeutic products around the same target
  - Multiple partnership opportunities
  - Extensively validated technology (clear MOA, over 500 publications)
  - Meaningful preclinical validation (target conserved)
  - Early cash flow from hair growth products
  - Entering clinical stage with phase I trials commencing 4Q2012 (antibody) and 1Q2013 (AMI)
- **Significant upside**
  - Antibody drug targets disease indications with major markets and unmet medical needs (kidney failure, COPD and surgical adhesion)
  - Midkine protein therapy targets very large markets (AMI, MI, stroke)

# Investment highlights

- **Powerful patent position**
  - Exclusive owner of novel target (midkine) for diagnosis and treatment of cancer, autoimmune diseases and cosmeceuticals
  - 21 patent families, 71 patents
  - **Key patent families:**
    - MK for the early detection and prognosis of cancers
    - Anti-MK agents to treat autoimmune & inflammatory diseases and cancers
    - MK to treat heart & brain ischemia
    - Production of MK
    - Anti-MK antibodies
- **Extensive knowledge base around midkine**
  - Over 250 peer-reviewed publications by Cellmid inventors
  - Discoverers of MK retained as advisors to Cellmid
  - Biannual MK conference
- **Large inventory including**
  - 3g of purified MK protein at the retail value of $7M
  - Five humanized monoclonal antibodies
  - Over 20 mouse monoclonal antibodies

# Board and management

- David King (Chairman)
- Maria Halasz (CEO and Managing Director)
- Robin Beaumont (Non-executive Director)
- Darren Jones (Head of Product Development)

# Thank you

**Maria Halasz**

**Chief Executive Officer**

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