Summary

- Midkine (MK) is a novel pro-angiogenic factor with high therapeutic potential, either as a target to inhibit blood vessel growth or as a factor to promote it.
- Cellmid Ltd has developed >100 murine anti-MK monoclonal antibodies and humanised three of these. Lead humAb CAB102 blocked angiogenesis in a preclinical tumor xenograft model. Anti-MK therapy is a promising approach to controlling angiogenesis in both cancer and non-cancer indications.
- Recombinant human MK promotes neo-vascularisation in vivo animal models of cardiac damage; MK itself represents a potential therapeutic for tissue damage and ischemic disease settings.

Midkine (MK)

- Discovered in 1988
- Subject of over 700 publications
- Retinoic acid-inducible heparin binding growth factor
- Prominent in embryogenesis, free MK barely detectable in healthy adults
- 13kDa protein (121 amino acids) with two domains
- Biological activities include:
  - Promoting angiogenesis
  - Inhibiting apoptosis
  - Facilitating cell migration
  - Promoting inflammatory cell infiltration
  - Promoting cell growth and differentiation

Highly basic 13kDa (121aa) protein
2 functional domains + flexible hinge
Single isoform

*Published review “Midkine” -Ad Fields-April 2010

MK is clinically implicated in angiogenesis

- Tumor biopsies: MK expression correlates with increased angiogenesis

**MK is a potent inducer of angiogenesis**

MK is as potent as VEGF at inducing angiogenesis

Exogenous MK induces neo-vascularisation in vivo

Model: Lewis rat
- Donor: Single into cardiac MK injection 14 days post-infarct
- Assessment: 5 weeks post-infarct
- MK treated: ~60% increased vascularization

Fukui et al 2008

Anti-MK interventions suppress tumor angiogenesis

Cellmid’s anti-MK mAb IP14 reduced angiogenesis (and tumor volume) in a prostate cancer xenograft model

Angiogenesis: tumor imaging (17 days post treatment)

Prostate cancer imaging xenograft model: Nude mice s.c. xenograft (PC-3 GFP cell line; AntiCancer, San Diego, USA). Mice dosed 25mg/kg IP injection 24h post s.c. implant, then 2 x weekly.

Tumor blood vessel density (17 days post treatment)

IP14 successfully humanised (“CAB102”) ~40g CAB102 produced (non-GMP)
Toxicology and tissue x-reactivity studies underway

Small molecule MK inhibitor (IMDK) suppressed angiogenesis in vivo even with continued high VEGF expression

Model: NSCLC xenograft model: H469 cells were injected s.c. with matrigel. Treatment with IMDK (p. 9mg/kg) commenced 14 days after tumor injection at either 3x or 5x per week. Tumor growth was measured 2-3 weeks each time and then termination (after 10 days of treatment).

**Midkine: a novel and highly potent pro-angiogenic factor**

Darren R Jones*, Joseph Haklani and Maria J Halasz

Cellmid Ltd, 15 Castlereagh St, Sydney, NSW, 2000, Australia

*Corresponding author: jones@cellmid.com.au

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