Cellmid (CDY)

COMPANY REPORT

It's rare for one company to own a whole new target this big

- **Company description.** Cellmid is a biotech company being built around midkine, a protein known to contribute to various diseases including cancer, heart disease and inflammation. Cellmid intends to go to the clinic in 1HCY 15 with an anti-midkine antibody in cancer and has a number of licensing agreements regarding the use of midkine as a cancer diagnostic. Cellmid also owns growing business selling hair restoration products.
- **It's rare for one company to own a whole new target this big**. Ordinarily, biotech companies differentiate themselves through the kind of drugs they have developed against targets that have been validated by others. By contrast, investors in Cellmid effectively control, through a comprehensive patent portfolio, a new target in midkine that is relevant across a wide range of diseases including heart disease and kidney disease, as well as cancer.
- **Cellmid intends to go to the clinic in the first half of 2015 with an anti-midkine antibody in cancer**. Given midkine's multiple roles in cancer progression across a range of tumours we see strong upside for this programme, especially since there is so much demand for new cancer antibodies from Big Pharma. Cellmid expects to read out data next year from its first Phase I/II study in cancer patients.
- **Cellmid is a player in personalised cancer medicine.** Cancer treatment is increasingly becoming 'personalised', meaning that drugs are being developed specific for subgroups within a patient population and administered depending on whether or not the patient expresses particular biomarkers. We expect midkine to be such a biomarker, which means that Cellmid already has the companion diagnostic for a future therapy, making it easier for the company to do business with Big Pharma.
- **Cellmid has various near-term revenue opportunities**, including three licensees for midkine diagnostics, and the hair regrowth business, which covers a lot of the company's R&D expense. We like the way in which CEO, Maria Halasz and her team have created these opportunities without neglecting the medium and long term opportunities from midkine.
- **Cellmid is undervalued on our numbers.** We value Cellmid at $0.08 base case and $0.30 optimistic case using a probability-weighted DCF approach (previously $0.07/$0.26, before we rolled forward our numbers at 30 June, increasing our valuation range). Our target price of $0.08 sits at our base case.

INVESTMENT SUMMARY

Year End: 30 June		2013 (A)	2014 (A)	2015 (E)	2016 (E)	2017 (E)
Revenue	$mn	1	2	15	25	28
EBITDA	$mn	-2.3	-2.2	1.8	11.8	13.1
EBIT	$mn	-2.4	-2.3	1.8	11.8	13.1
Reported Profit	$mn	-1.5	-1.5	1.9	12.0	12.4
Adjusted Profit	$mn	-1.5	-1.5	1.9	12.0	12.4
EPS (Reported)	¢	-0.2	-0.1	0.2	1.0	1.5
EPS (Adjusted)	¢	-0.2	-0.1	0.2	1.0	1.5
EPS Growth	%	N/A	N/A	N/A	N/A	40.0
PER (Reported)	x	N/A	N/A	17.7	2.8	2.0
PER (Adjusted)	x	N/A	N/A	17.7	2.8	2.0
Dividend	¢	0.0	0.0	0.0	0.0	0.0
Yield	%	0.0	0.0	0.0	0.0	0.0
Franking	%	0	0	0	0	0

RECOMMENDATIONS

Rating	**BUY** ▲
Risk	High
Price Target	**$0.08**
Share Price	$0.03

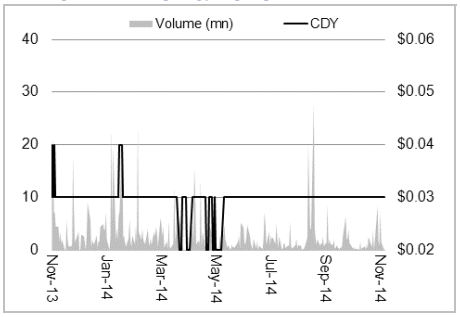
SNAPSHOT

Monthly Turnover	$0.9mn
Market Cap	$21mn
Shares Issued	736.2mn
52-Week High	$0.04
52-Week Low	$0.02
Sector	Health Care

BUSINESS DESCRIPTION

Cellmid is being built around midkine, a protein known to contribute to various diseases including cancer, heart disease and inflammation. Cellmid intends to go to the clinic in the first half of 2015 with an anti-midkine antibody in cancer and has a number of licensing agreements with diagnostics developers on the use of midkine as a cancer diagnostic. Cellmid also owns a small but growing business selling hair restoration products.

12-MONTH PRICE & VOLUME



RESEARCH ANALYST

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Disclosure
The author owns no shares in CDY.

Financial summary

Code	CDY
Analyst	Stuart Roberts
Date	24 November, 2014
Share price	$0.029
Market capitalisation	$21m
Year end	30 June

Rating	BUY
Price target	$0.08
Upside/downside	175.9%
Valuation	$0.079 / $0.301
Valuation method	Probability-weighted DCF
Risk	High

PROFIT AND LOSS (A$m)

Y/e June 30 (A$m)	FY13A	FY14A	FY15E	FY16E	FY17E
Revenue	0.5	2.2	14.7	25.3	27.9
EBITDA	**-2.3**	**-2.2**	**1.9**	**11.8**	**13.1**
D&A	0.0	-0.1	0.0	0.0	0.0
EBIT	**-2.4**	**-2.3**	**1.9**	**11.8**	**13.1**
Net interest	0.0	0.1	0.1	0.2	0.5
Pre-tax profit	**-2.3**	**-2.2**	**1.9**	**12.0**	**13.6**
Tax	0.8	0.7	0.0	0.0	-1.2
NPAT	-1.5	-1.5	1.9	12.0	12.4
Minority interests	0.0	0.0	0.0	0.0	0.0
Net profit after minorities	-1.5	-1.5	1.9	12.0	12.4

BALANCE SHEET (A$m)

Y/e June 30	FY13A	FY14A	FY15E	FY16E	FY17E
Cash	1.8	2.5	6.9	18.9	31.6
Current receivables	0.3	0.2	0.8	1.1	1.0
Inventories	1.7	1.7	2.2	2.5	2.5
Other current assets	0.1	0.1	0.1	0.1	0.1
Current assets	**3.8**	**4.5**	**10.0**	**22.6**	**35.2**
PPE	0.1	0.0	0.0	0.0	0.0
Intangible assets	2.2	1.9	1.9	1.9	1.9
Other non-current assets	0.0	0.0	0.0	0.0	0.0
Non-current assets	2.2	2.0	2.0	2.0	2.0
Total assets	6.0	6.5	11.9	24.5	37.2
Payables	0.5	0.6	0.9	1.1	1.1
Debt	0.0	0.0	0.0	0.0	0.0
Other liabilities	0.2	0.2	0.2	0.2	0.2
Total liabilities	0.7	0.8	1.1	1.3	1.3
Shareholders' equity	5.3	5.7	10.8	23.2	35.9
Minorities	0.0	0.0	0.0	0.0	0.0
Total shareholders funds	**5.3**	**5.7**	**10.8**	**23.2**	**35.9**
Total funds employed	**6.0**	**6.5**	**11.9**	**24.5**	**37.2**
W/A shares on issue	563.8	696.6	835.6	835.6	835.6

CASH FLOW (A$m)

Y/e June 30	FY13A	FY14A	FY15E	FY16E	FY17E
NPAT plus discontinued ops.	-1.5	-1.5	1.9	12.0	12.4
Non-cash items	0.0	0.1	0.4	0.4	0.4
Working capital	0.1	-0.4	-0.7	-0.4	0.0
Other operating cash flow	0.0	-0.4	0.0	0.0	0.0
Operating cashflow	**-1.5**	**-2.2**	**1.6**	**12.0**	**12.8**
Capex	0.0	0.0	0.0	0.0	0.0
Investments	0.1	1.0	0.0	0.0	0.0
Other investing cash flow	-0.8	0.0	0.0	0.0	0.0
Investing cashflow	**-0.7**	**1.0**	**0.0**	**0.0**	**0.0**
Change in borrowings	0.0	0.0	0.0	0.0	0.0
Equity raised	2.9	2.0	2.9	0.0	0.0
Dividends paid	0.0	0.0	0.0	0.0	0.0
Other financing cash flow	0.0	0.0	0.0	0.0	0.0
Financing cashflow	**2.9**	**2.0**	**2.9**	**0.0**	**0.0**
Net change in cash	**0.7**	**0.8**	**4.4**	**12.0**	**12.8**
Cash at end of period	1.8	2.5	6.9	18.9	31.6

EARNINGS (A$m)

Y/e June 30	FY13A	FY14A	FY15E	FY16E	FY17E
Net profit ($m)	-1.5	-1.5	1.9	12.0	12.4
EPS (c)	-0.3	-0.2	0.2	1.4	1.5
EPS growth (%)	N/A	N/A	N/A	524%	3%
P/E ratio (x)	-10.6	-13.6	12.6	2.0	2.0
CFPS (c)	-0.3	-0.3	0.2	1.4	1.5
Price/CF (x)	-11.3	-9.0	15.3	2.0	1.9
DPS (c)	0.0	0.0	0.0	0.0	0.0
Yield (%)	0.0%	0.0%	0.0%	0.0%	0.0%
Franking (%)	N/A	N/A	N/A	N/A	N/A
EV/EBITDA	-8.4	-9.1	10.6	1.7	1.5
EV/EBIT	-8.4	-8.7	10.7	1.7	1.5

PROFITABILITY RATIOS

Y/e June 30	FY13A	FY14A	FY15E	FY16E	FY17E
EBITDA/revenue (%)	-431.9%	-100.4%	12.7%	46.7%	47.0%
EBIT/revenue (%)	-435.1%	-105.6%	12.6%	46.7%	47.0%
Return on assets (%)	-25.7%	-22.9%	16.1%	49.0%	33.2%
Return on equity (%)	-29.0%	-26.1%	17.8%	51.8%	34.4%
Return on funds empl'd (%)	-29.0%	-26.1%	17.8%	51.8%	34.4%
Dividend cover (x)	N/A	N/A	0%	0%	0%
Effective tax rate (%)	33.8%	33.5%	0.0%	0.0%	9.0%

LIQUIDITY AND LEVERAGE RATIOS

Y/e June 30	FY13A	FY14A	FY15E	FY16E	FY17E
Net debt/(cash) ($m)	-2	-3	-7	-19	-32
Net debt/equity (%)	-33.1%	-44.2%	-64.2%	-81.5%	-88.2%
Net interest cover (x)	N/A	N/A	N/A	N/A	N/A
Current ratio (x)	5.9	6.2	9.2	17.5	27.8

INTERIMS

Y/e June 30 ($m)	2H13A	1H14A	2H14A	1H15F	2H15F
Revenue	0	1	1	6	9
EBITDA	**-1**	**0**	**-2**	**-1**	**2**
D&A	**0**	**0**	**0**	**0**	**0**
EBIT	**-1**	**-1**	**-2**	**-1**	**2**
Net interest	**0**	**0**	**0**	**0**	**0**
Pre-tax profit	-1	-1	-2	-1	3
Tax	**0**	**1**	**0**	**0**	**0**
NPAT	-1	0	-2	-1	3
Minority interests	**0**	**0**	**0**	**0**	**0**
Net profit after minorities	-1	0	-2	-1	3

VALUATION

	Base	Optim.
Cancer therapeutic (A$m)	51.7	227.2
Cancer diagnostic (A$m)	15.9	58.7
Consumer Health (A$m)	11.6	52.8
Value of Cellmid technology	79.2	338.7
Value of tax losses	7.0	7.0
Underlying R&D cost	-9.6	-9.6
Cash now (A$m)	1.6	1.6
Cash from options and cash to be rai	13.7	13.7
Total value (A$m)	92.0	351.4
Total diluted shares (million)	1168.5	1168.5
Value per share	$0.08	$0.30
Valuation midpoint	$0.19	
Share price now (A$ per share)	$0.029	
Upside to midpoint	554.2%	

Introducing Cellmid (ASX: CDY)

- **Cellmid is building itself around midkine.** Midkine is a protein known to contribute to cancer, heart disease and inflammation. Cellmid intends to go to the clinic in the first half of 2015 with an anti-midkine antibody in cancer, and the company already has a number of licensing agreements with diagnostics developers on its use as a cancer diagnostic. Cellmid also owns a small but growing business selling hair restoration products.
- **Midkine is useful across a range of disease indications.** Midkine, often called simple 'mk' in the literature, is a small heparin-binding growth factor protein[1] that is important in embryonic development, and while almost undetectable in healthy adults, is highly expressed in cancer and autoimmune disorders. Significant elements of midkine include:
  - Its role in preventing apoptosis as well as in cell migration, angiogenesis and cell growth, which means that it works at various levels of cancer progression;
  - Its ability to up-regulate at the onset of inflammation, making it an ideal 'upstream' target in diseases such as diabetic nephropathy; and
  - Its involvement in the preservation and repair of injured tissue, suggesting a potential treatment for myocardial infarction.
- **Cellmid has positioned itself to dominate midkine**. Midkine was discovered in 1988 at Nagoya University by Professors Takashi Muramatsu and Kenji Kadomatsu[2]. Up until now midkine has not generally been referred to as a 'hot' new disease target, but the number of published papers in the field each year has grown steadily. Cellmid in effect positioned itself as the world leader in midkine research when it acquired privately-held, Cell Signals in 2008 for US$1.5m plus 20 million shares. The acquisition gave Cellmid a library of around 120 anti-midkine antibodies and a comprehensive patent portfolio protecting midkine and midkine antagonists globally.
- **Cellmid intends to go to the clinic in the first half of next year with an anti-midkine antibody in cancer**. Cellmid is currently pre-clinical with an antibody it believes will work particularly well in gastrointestinal and thoracic cancer. Given midkine's multiple role in cancer progression, the substantial published studies on human midkine expression in cancer patients, and the large body of animal studies to back it up, we see strong upside for this programme given the continued demand for new cancer antibodies from Big Pharma.
- **Cellmid has developed a suite of midkine diagnostics.** On evidence that midkine can be used to diagnose cancer at an early stage, Cellmid has been able to secure three licensees for midkine diagnostics. The first of these, a bladder cancer diagnostic developed by New Zealand biotech, Pacific Edge under license from Cellmid, was launched in the US in mid-2013. Cellmid will earn near-term revenue from Pacific Edge as well as from America's Quest Diagnostics, which has developed a lung cancer diagnostic; and from Japan's Fujikara, which is developing a diagnostic for early stage cancer.
- **Cellmid sees potential for midkine antagonists in inflammation**, with the company particularly focused on acute kidney injury and chronic kidney disease, as well as the prevention of surgical adhesions.
- **Midkine may prove useful in heart disease**, with evidence that midkine can help to shrink the size of a myocardial infarct and also prevent cardiac remodelling following the infarct. Given the continuing high incidence of AMI and heart failure we see strong partnering interest emerging for midkine in these indications.
- **Cellmid also owns a hair regrowth business**. In 2013 Cellmid acquired the global rights to évolis, a clinically validated hair regrowth product that works through inhibition of FGF-5. Cellmid had previously licensed the rights to Australia for this product in 2010. With no major hair regrowth product having been launched globally since the 1980s we see strong upside for the évolis range given the high level of hair loss in both sexes, and the science that lies behind Cellmid's product. Currently the business is small but Cellmid is building up its roster of global distribution partners for évolis.

Midkine is a relevant target in cancer, heart disease and inflammation.

[1] By small we mean only 13 kilodaltons or 121 amino acids in size. There are two midkine domains, called 'C' and 'N', with C traditionally regarded as the more interesting target although N is now emerging in importance (see Biochem J. 2013 May 1;451(3):407-15). Midkine has >90% amino acid identity between mammalian species (see Biochem Biophys Res Commun. 1991 Apr 30;176(2):792-7).
[2] Biochem Biophys Res Commun. 1988 Mar 30;151(3)1312-8.

Cellmid controls a new cancer target

- **Midkine is an ideal cancer target.** A protein is a particularly good cancer target if it is: a) expressed in many different kinds of tumours; b) not present in healthy people; and c) if it can be found to play a role in cancer at various stages. Midkine is ideal in this regard because:
  - The protein is expressed highly in various malignant tumours – Cellmid estimates at least 26 types[3] - but is almost absent in healthy people[4];
  - The protein inhibits apoptosis[5];
  - The protein promotes proliferation and migration in cancer[6]; and
  - The protein is involved in cancer angiogenesis[7].
- **We know from the literature that midkine antagonists work in cancer**. Consider just three papers:
  - Takei et. al. showed in 2001 that antisense oligonucleotides to midkine were highly effective at suppressing tumour growth in a mouse model of rectal carcinoma[8];
  - Sueyoshi et. al. showed in 2011 that midkine antibodies inhibited primary tumour growth and slowed metastasis in a xenograft model of osteosarcoma [9]; and
  - Kishida et. al. showed in 2012 that a midkine aptamer strongly suppressed neuroblastoma tumour growth in a mouse xenograft model[10].
- **So how come there are no anti-midkine drugs in the clinic yet?** Midkine was first discovered in 1988, however up until now no drug development company had pursued its cancer therapeutic possibilities. We see three reasons for this:
  - Much of our knowledge about midkine has only emerged in the last five years;
  - Until recently most research interest in midkine had been in Japan, making it harder for the target to get noticed; and
  - Comprehensive control of the relevant intellectual property by Cellmid or its predecessor company Cell Signals, which Cellmid acquired in 2008, inhibited other groups from entering the field[11].
- **Cellmid will be in the clinic with a midkine antibody in cancer from the first half of 2015**. The company started humanising midkine monoclonal antibodies from its library in 2011 and by May 2014 had selected a lead candidate called CAB102 to take to the clinic. This candidate, in xenograft studies, shrunk non-small cell lung cancer tumours by 50% over 21 days in conjunction with carboplatin ($p<0.01$ versus carboplatin only). Cellmid intends to start a 12-patient open label dose-escalation study of CAB102 in multiple solid tumours from the first half of 2015, recruiting colorectal, lung and gastric cancer patients. The trial would likely yield interim data in mid-to-late 2015.

Cellmid will have interim data from its first anti-midkine cancer trial next year.

- **Cellmid is an emerging cancer antibody play**. Antibodies make great cancer drugs because of their exquisite specificity, low side effects and their synergies with existing chemotherapies. This has caused cancer antibodies to grow into a large drug class featuring blockbusters such as Roche's Rituxan[12] (US$7.5bn in net sales in 2013), Avastin[13] (US$6.7bn) and Herceptin[14] (US$6.6bn). As a consequence of this success, Big Pharma is very comfortable with having many cancer antibodies in its pipeline. We therefore see potential for a licensing deal in the cancer spaces once the data comes in from the initial study.
- **Cellmid thinks it can develop a good 'trispecific' antibody**. In April 2014 Cellmid announced that it had retained the Lisbon-based Biotecnol, an antibody developer[15], to

[3] See the company's 31 March 2014 presentation, slide 16.
[4] See Br J Pharmacol. 2014 Jun;171(12):2925-39. Epub 2014 Jan 27. This paper is authored by Darren Jones, Cellmid's Head of Product Development.
[5] See PLoS One. 2013 Aug 16;8(8):e71093.
[6] See Mol Cancer Res. 2014 May;12(5):670-80. Epub 2014 Feb 24.
[7] See Cancer Res. 1997 May 1;57(9):1814-9.
[8] Cancer Res. 2001 Dec 1;61(23):8486-91.
[9] See Cancer Lett. 2012 Mar;316(1):23-30. Epub 2011 Oct 20.
[10] See Cancer Res. 2013 Feb 15;73(4):1318-27. Epub 2012 Dec 14.
[11] It's worth noting that Amgen has paid attention in recent years - see Neoplasia. Apr 2008; 10(4): 340–346.
[12] Generic name rituximab, see www.rituxan.com. Rituxan gained FDA approval in November 1997.
[13] Generic name bevacizumab, see www.avastin.com. Avastin gained FDA approval in February 2004.
[14] Generic name trastuzumab, see www.herceptin.com. Herceptin gained FDA approval in September 1998.
[15] Private held, www.biotecnolgroup.com. Biotecnol's Rodon Biologics unit previously humanised some of Cellmid's midkine antibody candidates and will manufacture the CAB102 antibody which goes to the clinic in 2015.

develop 'Tribodies' that could target midkine as well as additional oncogenic proteins like checkpoint inhibitors[16]. Given the rising popularity of antibodies that have the ability to hit more than one target – Amgen bought Micromet for US$1.16bn in early 2012 in order to lead the bispecific cancer antibody space – we see strong potential for this programme[17].

- **Cellmid is a player in personalised cancer medicine.** Increasingly cancer treatment is becoming 'personalised', meaning that drugs are being developed specific for subgroups within a patient population and administered depending on whether or not the patient expresses particular biomarkers. Cellmid's anti-midkine antibody is in our view likely to be a future personalised cancer medicine, prescribed only to patients having elevated midkine, as determined by a midkine diagnostic which the company has already invented.

Herceptin is a US$6.6bn pa personalised cancer medicine.

- **The era of personalised cancer medicine is here and is big business, as the record of Herceptin has amply shown**. Herceptin was a US$6.6bn best-seller for Roche in 2013, but it only worked for Her2-positive breast cancer, which is around 20% of all breast cancer. Other personalised cancer drugs have followed in Herceptin's wake:
  - Roche's Tarceva[18], AstraZeneca's Iressa[19] and Boehringer Ingelheim's Gilotrif[20] only work in NSCLC patients who have tumours with EGFR mutations, which is around 10-15% of all patients. Tarceva was a US$1.4bn drug in 2013 and Iressa had US$647m in 2013 sales;
  - Roche's Zelboraf[21] and GSK's Tafinlar[22] for metastatic melanoma only work in patients that have the BRAF V600E mutation in their tumour, which is 40-50% of malignant melanoma;
  - GSK's Mekinist[23], also for metastatic melanoma is approved in patients that have both BRAF V600E and BRAF V600K mutations; and
  - Pfizer's Xalkori[24] for non-small-cell lung cancer (LSCLC), only works for patients whose tumours carry the EML4-ALK fusion gene. That's a mere 3-7% of all NSCLC.
- **Having a biomarker and a companion diagnostic today makes it easier for Cellmid to attract investors and do business with Big Pharma**. The trouble with personalised cancer medicine, from the perspective of an early stage company, is that generally the early clinical studies of a drug are the ones which define what biomarkers are appropriate, after which the clinical studies can be enriched for patients expressing the biomarkers. The rise of adaptive design in cancer studies makes this relatively easy from a regulatory standpoint, but it still often means a study in which the drug fails from an 'all comers' perspective but works for the patients that have the biomarkers[25]. Investors don't tend to like this, and Big Pharma has reason to be cautious until the first biomarker-enriched cohort studies yield data. Given that Cellmid already has both the biomarker and a diagnostic for it, the company has a strong advantage over other would-be personalised cancer drug developers.

[16] The 'checkpoints', a relatively new group of cancer targets, are protein kinases controlling the cellular response to DNA damage. Checkpoint inhibitors are therefore potentially useful in potentiating chemotherapy drugs that work by damaging the DNA of cancer cells.
[17] Other companies involved in bispecific antibodies include Genmab, Immunomedics and Xencor.
[18] Generic name erlotinib, see www.tarceva.com. Tarceva gained FDA approval in November 2004.
[19] Generic name gefitinib, see www.iressa.com. Iressa gained FDA approval in May 2003.
[20] Generic name afatinib, www.gilotrif.com. Gilotrif gained FDA approval in July 2013.
[21] Generic name vemurafenib, see www.zelboraf.com. Zelboraf gained FDA approval in August 2011.
[22] Generic name dabrafenib, see www.tafinlar.com. Tafinlar gained FDA approval in May 2013.
[23] Generic name trametinib, see www.trametinib.com. Like Tafinlar, Mekinist also received FDA approval in May 2013.
[24] Generic name crizotinib, see www.xalkori.com. Xalkori gained FDA approval in August 2011.
[25] For a good example, see the 26 November 2013 release from Merrimack Pharmaceuticals (Cambridge, Ma., Nasdaq: MACK, www.merrimackpharma.com). headlined '*Merrimack Pharmaceuticals' MM-121 Demonstrates Positive Signal in Two Phase 2 ER/PR+ Breast Cancer Studies'*. Basically this study saw MM-121 miss its primary endpoint but look encouraging in terms of two biomarkers.

Cellmid also controls a new inflammation target

- There is a large body of work showing midkine to be a driver of inflammation and that antagonists of midkine are anti-inflammatory. Consider three prominent examples from the literature[26]:
  - **Rheumatoid Arthritis**. In 2004 Maruyama showed, in a mouse model of RA, that midkine knockout mice seldom developed RA, while most of the wild-type mice did[27];
  - **Multiple Sclerosis**. In 2008 Wang et. al. were able to show that anti-midkine aptamers could alleviate experimental autoimmune encephalomyelitis – the standard animal model for MS – by expanding the regulatory T cell population[28]; and
  - **Kidney inflammation**. In 2005 Sato et al. showed that kidney inflammation and damage were suppressed when mice were given anti-midkine oligos.[29]
- **There are three inflammatory indications that Cellmid are going after in midkine**, namely kidney (for both acute kidney injury and chronic kidney disease), lung (as a potential COPD treatment) and surgical adhesion.

Cellmid may have the Next Big Thing in kidney disease

- **There is ample pre-clinical evidence that midkine antagonists would work in kidney disease**:
  - In 2001 Sato et al. showed that midkine facilitated neutrophil infiltration in ischemic renal injury[30];
  - In 2006 and 2007 by Kosugi et. al. showed that midkine is a key driver in the pathogenesis of diabetic nephropathy[31]; and
  - In 2011 Kato et. al. showed that midkine-drive neutrophil infiltration was involved in the protein overload model of acute kidney injury[32].

Around 11% of the US adult population has chronic kidney disease.

- **The markets for kidney disease are large, growing and underserved**:
  - There are perhaps 800,000 acute kidney injuries in the US annually that require renal replacement therapy[33];
  - 11% of the US adult population or 26 million people have chronic kidney disease[34], driven by the rapid rise of diabetes prevalence; and
  - There are no on-market specific therapies, beyond steroids.
- **Cellmid has various renal indications in mind for midkine antibodies, including**:
  - Preservation of kidney function in an environment of multi-organ failure, something that happens during sepsis. One study has suggested that up to 25% of hospitalised patients in the US experience acute kidney failure[35];
  - Chemotherapy-related nephrotoxicity, which can be a serious issue with some cancer treatments, affecting for example, 5-10% of patients on the chemotherapy drug cisplatin[36];
  - Diabetic nephropathy, a problem for around a third of all diabetics[37]; and
  - Glomerular sclerosis, which could allow Cellmid to gain Orphan Drug status - in the US perhaps 70,000 people have the most common type of this condition, called Focal Segmental Glomerulosclerosis[38].

[26] There are many others. Consider, for example, the work of Narita et. al., who in 2008 showed that midkine is expressed by infiltrating macrophages in in-stent restenosis, making midkine antibodies potentially very valuable in preventing such restenosis. See J Vasc Surg. 2008 Jun;47(6):1322-9. Epub 2008 Mar 19.
[27] See See Arthritis Rheum. 2004 May;50(5):1420-9.
[28] See Proc Natl Acad Sci U S A. 2008 Mar 11;105(10):3915-20. Epub 2008 Mar 4.
[29] See Kidney Int. 2005 Apr;67(4):1330-9.
[30] See J Immunol. 2001 Sep 15;167(6):3463-9.
[31] See Lab Invest. 2007 Sep;87(9):903-13. Epub 2007 Jul 2.
[32] See Clin Exp Nephrol. 2011 Jun;15(3):346-54. Epub 2011 Mar 1.
[33] Estimated from Crit Care Med. 2008 Apr;36(4 Suppl):S146-51.
[34] Source: NHANES data, see Am J Kidney Dis. 2003 Jan;41(1):1-12.
[35] See Ann Pharmacother. 2002 Jul-Aug;36(7-8):1261-7.
[36] See World J Gastroenterol. Aug 14, 2011; 17(30): 3510–3517.
[37] Consider that ~20-30% of previously diagnosed diabetics have microalbuminuria (see Am J Kidney Dis. 2002 Mar;39(3):445-59), the earliest stage of nephropathy. Around 5% will have macroalbuminuria and 0.8% elevated plasma creatinine, where the kidney is failing and the annualised risk of death is ~20% (see Kidney Int. 2003 Jan;63(1):225-32).

There are many other indications that Cellmid can go after in inflammation.

- Cellmid is focused on getting its first cancer indications underway before it focuses on inflammation. That said, there are two other areas beyond kidney disease where the company thinks it can make a difference:
  - **COPD.** Recent work has shown the feedback loop that exists between the lung and the kidney[39] (which Hobo et. al. have shown[40]) is mediated by an enzyme called ACE, a cause of hypertension. Midkine is therefore potentially useful in treating lung damage driven by kidney damage, which would be useful in COPD patients with kidney disease. One study has suggested that 5-10% of COPD patients have undiagnosed renal failure[41]; and
  - **Surgical adhesion.** Abdominal adhesions are bands of fibrous tissue that can form between abdominal tissues and organs, causing them to stick together. Often this is caused by inflammation related to surgery. Inoh et. al. have shown that midkine plays a key role in these adhesions, so that anti-midkine antibodies could assist in their prevention[42]. Around half of all abdominal surgery typically features adhesions[43], which is significant given that there are more than a million abdominal procedures in the US each year[44].

Midkine is useful in heart attack and heart failure

- **Midkine can treat heart attacks and prevent heart failure.** Midkine is well-known as a facilitator of plaque formation after heart/vascular surgery. There is ample evidence that midkine with reparative activity forms after a myocardial infarction[45]. Cellmid has pre-clinical evidence, from pig and mouse models, that midkine can reduce the damage from myocardial and cerebral infarct by preventing apoptosis and increases blood vessel formation:
  - Horiba et. al showed in 2006 that a midkine injection in midkine knockout mice could significantly reduce infarct size[46];
  - Fujkui et al. showed in 2008 that even delayed administration of midkine could still attenuate cardiac remodelling after myocardial infarction[47]; and
  - Ishiguro et. al showed in 2011 that intracoronary injection of midkine could cut ischemia/reperfusion injury in pigs[48].

Midkine can repair the damage from a heart attack

- **There are a lot of heart attacks and heart failure out there**. In the US there will be around 720,000 heart attacks this year for people over 35[49], while around 5.1 million people, or ~2% of the population over 20, will enter heart failure[50].
- **A proof of concept study for heart attack was completed in April 2011**. Cellmid has completed various pre-clinical studies in AMI and, as with inflammation, we expect that the midkine programme will move forward once Cellmid has some momentum in the use of midkine in cancer.

[38] This was the disease which stunted the growth of the American actor Gary Coleman (1968-2010), famous for playing Arnold in the 1980s situation comedy Diff'rent Strokes.
[39] See Nephrol Dial Transplant. 2010 Jan;25(1):32-4. Epub 2009 Sep 15.
[40] See J Clin Invest. 2009 Jun;119(6):1616-25. Epub 2009 May 18.
[41] See Respir Med. 2012 Mar;106(3):361-6. Epub 2011 Nov 29.
[42] See Biochem Biophys Res Commun. 2004 Apr 23;317(1):108-13.
[43] See Surg Today. 2014 Mar;44(3):405-20. Epub 2013 May 9.
[44] See J Am Coll Surg. 2004 Nov;199(5):762-72.
[45] See Anticancer Res. 1998 Jan-Feb;18(1A):145-52.
[46] See Circulation. 2006 Oct 17;114(16):1713-20. Epub 2006 Oct 2.
[47] See Ann Thorac Surg. 2008 Feb;85(2):562-70.7
[48] See Front Physiol. 2011 Jun 23;2:27.
[49] Source: American Heart Association, Heart Disease and Stroke Statistics, 2014 Update, Table 18.1.
[50] Source: American Heart Association, Heart Disease and Stroke Statistics, 2014 Update, Table 19.1.

Midkine makes for great diagnostics

- **Midkine makes for a great cancer diagnostic**. We noted above that serum midkine is elevated in many different types of cancer but what makes a midkine antibody a great cancer biomarker is evidence that it is elevated in the very early stages. Various studies have suggested that midkine antibodies could be much more specific for cancer diagnosis than other, better-known biomarkers:
  - In one early study, midkine was able to detect 45% of breast cancer at 'Stage 0', where the cancer is only located at the point where it started, whereas antibodies for three biomarkers couldn't detect any[51];
  - In 2003 Ikematsu et. al. showed that midkine could be used to diagnose the correct stage of neuroblastoma severity[52];
  - In 2003 Shimada et. al. showed that midkine serum concentration greatly enhanced disease detection over conventional markers in esophageal cancer patients [53];
  - In 2003 Shimada et. al. showed that serum midkine could function as an effective prognostic marker for esophageal cancer[54]; and
  - In 2009 Ibusuki et. al. showed that the same approach worked in breast cancer[55].
- **Midkine has diagnostic applications well beyond cancer**. When Cellmid acquired Cell Signal in 2008 the company had developed diagnostics for early detection of cancer as well as for diagnosis of Rheumatoid Arthritis, Alzheimer's disease[56] and Sjögren's syndrome.
- **Cellmid has developed a midkine ELISA** which was launched in November 2010 for use in research applications. This ELISA, which has an 8 pg/mL limit of detection, well within the range of healthy serum midkine levels that can run as high as 1,000 pg/mL[57], gained its CE Mark in 2011.
- **There have been three diagnostic licensing deals since 2009**, one of which is now generating royalties for Cellmid:
  - A diagnostic for early detection of lung cancer was licensed to Celera in October 2009 and Quest Diagnostics[58], which bought Celera in 2011 for US$344m, is currently doing clinical validation work[59]. Under the 2009 licence, Celera/Quest has exclusive use of midkine as a long cancer diagnostic until October 2014, but after that date Cellmid can license other parties. Cellmid expects an update on Quest's progress in March 2015;
  - A bladder cancer diagnostic was licensed to Pacific Edge[60] in May 2010 and launched in the US in March 2013; and
  - Coming soon is a midkine early cancer diagnostic, licensed to Japan's Fujikara Kasei[61].
- **Cellmid now knows what healthy serum midkine should be**, thanks to a two year study conducted by Japan's Kumamoto University called 'CK3000'. This study screened 574 healthy volunteers – as determined by various other biomarkers and extensive lifestyle data – between 2011 and 2013, and found that normal levels of the protein were under 1,000 pg/mL. For the 2.7% of screened subjects with concentrations above this level, the investigators were able to follow up six and found that four of the six had previously been hospitalised for cancer or inflammatory disorders. We expect this study, yet to be published, will contribute to more diagnostics being developed.
- **Cellmid's diagnostic work is relevant to the cancer therapeutic programme**, since a successful drug will, like Herceptin and other cancer drugs, need a companion diagnostic before a patient went on the drug.

Pacific Edge launched its bladder cancer diagnostic from Cellmid in mid-2013.

[51] See Cellmid's 9 May 2008 presentation, slide 19. The biomarkers were CA15-3, BCA225 and CEA.
[52] Cancer Res. 2001 Dec 1;61(23):8486-91.
[53] See Oncol Rep. 2003 Mar-Apr;10(2):411-4. The markers were p53 antibodies, CEA, SCC and CYFRA.
[54] See Cancer Sci. 2003 Jul;94(7):628-32.
[55] See Cancer Sci. 2009 Sep;100(9):1735-9. Epub 2009 Jun 1. The markers were CA15-3, CEA and NCCST-439.
[56] Yasuhara et. al. showed in 1993 that midkine is present in senile plaques of Alzheimer's Disease. See Biochem Biophys Res Commun. 1993 Apr 15;192(1):246-51.
[57] Cellmid has reported that the inter-assay CV of its ELISA is less than 25% and that the test was accurate with a recovery range of between 75% and 125%. Moreover there was no cross-reactivity to pleiotrophin or other serum components.
[58] Madison, NJ, NYSE: DGX, www.questdiagnostics.com.
[59] For data on the sensitivity and specificity of the test see Slides 30 and 31 of Cellmid's 30 September 2011 presentation. Quest is participating in the NCI's chest X-Ray screening Prostate, Lung, Colorectal and Ovarian Trial (PLCO) as part of the clinical validation programme.
[60] Dunedin, New Zealand, NZX: PEB, www.pacificedge.co.nz.
[61] See www.fkkasei.co.jp.

Cellmid is in the hair regrowth business

- **Cellmid started selling hair regrowth products in 2010**. In the course of doing business in Japan, Cellmid was introduced in 2010 to a company called Advangen, which had developed various hair regrowth product based on FGF-5, a protein expressed by macrophage-like cells in the scalp that transitions hair follicles from growth to rest phase. Cellmid licensed the rights to Advangen's products for Australia and New Zealand and started selling them in December 2010. Two years later, in May 2013, Cellmid acquired the global rights to the products for $1.2m cash and 55m Cellmid shares.
- **There is real science behind the products.** Antagonising FGF-5 is well known to promote hair growth[62] and, since FGF-5 has no other known functions, it's reasonable to say that FGF-5 inhibitors are safe to use. Advangen's scientists had found that root extracts from two plants (*Sanguisorba officinalis* and *Eriobotrya japonica*) had anti-FGF-5 activity, and from these actives they had created three products – 'Jo-Ju Shampoo', Jo-Ju Scalp Lotion' and 'Lexilis Scalp Lotion'. A paper on the *S. officinalis* extracts is available online[63].
- **évolis is a Cellmid-created brand**. Initially Cellmid took the Advangen intellectual property and prepared its own FGF-5-based hair regrowth product which it branded évolis. The product gained a TGA listing and launched commercially in 2012.
- **The data for évolis is good**, with Cellmid's own clinical study showing a 21% increase in the rate of hair growth and a 35% reduction in hair loss. 74% of users found the product beneficial. There are multiple channel partners for the product, including online[64].

évolis is good for a 21% increase in the rate of hair growth.

- **There is big theoretical demand for hair regrowth products like évolis**. Androgenic alopecia – the technical name for common hair loss – affects both sexes[65]. While accurate numbers are hard to come by, we estimate around 30% of women and 60% of men are affected[66], which would mean around 100 million people in the US – 30 million women and 70 million men. This phenomenon has created two significant products in the last 25 years:
  - Propecia[67], an orally available a 5-alpha reductase inhibitor[68] from Merck & Co., gained FDA approval in 1992 as a treatment for benign prostatic hyperplasia[69], with an androgenic alopecia indication added five years later. Propecia lost US market exclusivity in January 2013. In 2012, its last full year of exclusivity, it was a US$242m product. Propecia has side effects that have deterred a lot of potential users[70]; and
  - Rogaine, available as a foam from J&J[71], lengthens the anagen (ie growth phase) of hair follicles. The drug originates from an old Upjohn blood pressure drug called Loniten, generic name minoxidil, which gained FDA approval in 1976. Noticing the effect on hair regrowth, Upjohn obtained an alopecia indication as Rogaine in 1988 and approval to sell over-the-counter in 1996. The product came into J&J's stable when Pfizer, Upjohn's eventual owner, sold its consumer products unit in 2006. It is, however, not a big seller – only US$31m in US sales in 2006[72] due to the fact that only around 20-25% of users see significant regrowth of the hair they have lost.
- **Cellmid is taking its hair regrowth business global with distributors being sought in key markets.** There was already Japanese distribution at the time of the Advangen acquisition in 2013. Cellmid now wants to sell worldwide. In January 2014 the company secured Chinese distribution via Huana Likang, a fast-growing direct marketing company with primary channels through television shopping networks and web-based sales. We expect other distribution agreements will follow as well as new products[73].
- **In FY14 revenue from product sales was $1.15m**. Cellmid's hair regrowth business may be small but it is growing – FY13 revenue was $0.54m. If nothing else, the products help to cut Cellmid's burn rate, which in the twelve months to September 2014 was only $360,000 per month.

[62] See Cell. 1994 Sep 23;78(6):1017-25. A recent PNAS paper has shown how mutations in FGF5 contribute to excessive eyelash growth (Proc Natl Acad Sci U S A. 2014 Jul 22;111(29):10648-53. Epub 2014 Jul 2).
[63] See www.advangen.com.au/scientific-publications.
[64] See www.evolisproducts.com.au.
[65] In spite of the name – 'andros' being the Greek word for 'men'. Specialists in the field often separate the condition into 'male pattern hair loss' and 'female pattern hair loss'.
[66] Estimated using data from J Investig Dermatol Symp Proc. 2005 Dec;10(3):184-9..
[67] Generic name finasteride, see www.propecia.com.
[68] 5-alpha reductase converts testosterone to 5 alpha-dihydrotestosterone (DHT). That hormone binds to receptors in scalp follicles and shrinks them.
[69] That is, enlargement of the prostate. BPH is androgen dependent, that is, driven by testosterone, and dihydrotestosterone is necessary for the hyperplasia to occur.
[70] Low libido, erectile dysfunction, decreased arousal and problems with orgasm – and this goes on at least two and a half years after you stop taking the drug. See J Sex Med. 2011 Jun;8(6):1747-53. Epub 2011 Mar 18.
[71] See www.rogaine.com.
[72] See *Rogaine Seeks Place in the Morning Routine* by Andrew Adam Newman, New York Times, 24/1/2008
[73] The company intends in 2015 to investigate the use of midkine in the treatment of alopecia.

Cellmid has started to attract licensing interest for therapeutics

- **Cellmid has optioned a midkine antibody to Zoetis**. Cellmid announced in November 2014 that it had granted the US animal health company Zoetis[74] an option to license one of its anti-midkine antibodies for therapeutic use in companion animals. Under the agreement, Zoetis has exclusive use of Cellmid's midkine antibodies in animals and will pay unspecified upfront and exclusivity payments until such time as the option to license is exercised.
- **Zoetis is an animal health major**. Zoetis is the former animal health unit of Pfizer, spun out of that company in 2013. Currently capitalised at US$22.4bn[75], Zoetis is the world's largest animal health company, with US$4.56bn in 2013 revenue and US$504m in NPAT. Its 2013 R&D expense was US$399m, or 8.8% of revenue. Zoetis believes that it has grown faster than the animal health market over the last three years. There are three reasons why the Zoetis collaboration is potentially valuable for Cellmid:
  - Zoetis is currently seeking to boost its exposure to products for companion animals, with the majority of its revenue coming from production animals at present. The November 2014 acquisition of assets from Abbott Animal Health was designed to bolster the companion asset portfolio, and the company has had a notable new product success in the form of Apoquel, for the treatment of canine pruritis;
  - With the company downgrading earnings forecasts in November 2014, and having funds associated with activist shareholder Bill Ackman owning 10% of the stock, Zoetis is under pressure to bring to market new products; and
  - Companion animals are a growing market opportunity, have generated most of the growth in the animal health market for some years now[76].
- **Success with Zoetis could open up other doors**. We believe that if the Zoetis option converts into a licence then other human licensing opportunities may emerge, given the homology between animal and human midkine and the de-risking that animal studies would present to a potential licensee in human applications.

Cellmid's collaborator Zoetis is the world's largest animal health company.

[74] Florham Park, NJ, NYSE: ZTS, www.zoetis.com.
[75] 18 November 2014 market close on NYSE.
[76] See *Animal-health pharmaceuticals are jumping the 'ethical channel'* by Bob Sperber, Pharmaceutical Commerce, 2/5/2013.

Valuing Cellmid – How we get 8 cents per share

- We valued Cellmid using a probability-weighted DCF approach. Previously (30 May 2014) we had valued Cellmid at $0.07 per share base case and $0.26 optimistic case. Our new valuation range is $0.08/$0.30.
- Our WACC was 14.1% (High risk)[77].
- We modelled payoffs for an anti-midkine cancer antibody, the cancer diagnostics and the suite of hair regrowth products.
- We model around 14 years of commercial exclusivity for the products followed by a negative 3-5% pa terminal growth rate. When we talk about 'Peak sales' we mean sales at year 14.
- We rolled forward our numbers at 30 June, resulting in the increase in our valuation range.

Risk weightings

- For the cancer antibody we used a 19% risk weighting for base case and 38% for optimistic case, to reflect the fact that the upcoming Phase I is in fact a Phase I/II with an easy lead-in to a full Phase II if the current study shows solid interim data in terms of response rates.
- For the cancer diagnostics and the consumer products we used no risk weightings. For the diagnostics, this is reasonable since Cellmid now knows what constitutes 'normal' serum midkine levels and there are multiple studies showing the effectiveness of a midkine diagnostic in cancer.

Commercial outcomes

- We assume that the cancer antibody licences in 2015-2016, for US$10-20m upfront, US$100-150m milestones and 10-14% royalties. We assume that the products launch by 2018-2019 and model peak sales of US$1.7-$2.2bn;
- We assume that the diagnostics can gain a further US$10-20m in upfronts and milestones by existing and future licensees. We model peak sales for all diagnostics of $170-$290m, with royalties ranging from 5% to 10%; and
- For the haircare products, we assume continued self-distribution with sales peaking at $13m-36m. We assume gross margins of between 50% and 70% is achievable over time.

Further capital

- We assume that the company raises $3m at $0.02 per share in order to complete the early clinical work on midkine in cancer.

How Cellmid can re-rate to our target price

- We see a number of potential re-rating events coming up over the next twelve months, including:
  - A pre-IND meeting with the FDA on the anti-midkine cancer programme;
  - Commencement of the Phase I/II;
  - First revenues from Pacific Edge related to the bladder cancer diagnostic;
  - New distribution agreements for évolis; and
  - Early clinical work on midkine in alopecia.

[77] For a relevant discount rate, we use WACCs of between ~12% and ~16% depending on the risk for Life Science companies. This is derived from a RFR of 3.7% (10 year bond at 30 May); a MRP of 7.5%-11.5% (7.5% for 'medium risk' companies, 9.5% for 'high risk' companies like Cellmid and 11.5% for 'speculative' companies); and an ungeared beta of 1.1 . We regard Life Science companies with existing businesses, or who have enough capital to reach the market with their products, as 'Medium' risk. Companies that have small revenue streams from marketed products but that are still potentially in need of capital are 'High' risk. Everything else is 'Speculative'.

Leadership

- **CEO Maria Halasz**, who has been CEO of Cellmid since April 2007, brought to the company decades of experience advising Life Sciences investors, including some time as a venture partner at the Emerging Technology Fund of venture capital firm, Allen & Buckeridge. Ms Halasz sourced the midkine projects for Cellmid in 2008 as well as the hair care businesses and has moved these ventures forward to the point where a midkine programme is about to go clinical. We like Ms Halasz's focus on near-term revenue opportunities for midkine as well as hair care, which has been executed without neglecting the medium and long term opportunities from midkine.
- **Darren Jones**, Head of Product Development, brings strong knowledge of antibodies, built through years of benchtop research in cellular immunology as well as companies such as Immune System Therapeutics[78].
- **Koichiro Koike**, General Manager, Japan, brings valuable contacts in Japan which has helped to facilitate the acquisition of the midkine programmes by Cellmid.
- **Emma Chen**, VP Business Development, brings strong smarts in hair care from her previous role as CEO of Ashley & Martin, an Australian chain of hair loss treatment clinics.
- **The Cellmid board**, which includes Maria Halasz, has the skills required to build a large biotech company. Chairman Dr David King brings corporate skills built over many years in the Australian resources sector. Graeme Kaufman has been involved with a number of successful Life Sciences companies in Australia including CSL[79] and Mesoblast[80]. And Martin Rogers was instrumental in rescuing the cancer immunotherapy company Prima Biomed[81] from oblivion in 2007 and taking it to Phase III by 2012.

Maria Halasz has brought in near-term revenue opportunities without neglecting the medium and longer term horizons.

The risks

- We see four major risks related to Cellmid:
  - **Revenue risk**. There is the risk that sales of évolis and revenue from the midkine diagnostics in the early years will be perceived as low, leading to general disappointment with Cellmid as a stock;
  - **Development risk**. There is the risk that the cancer and inflammation programmes of Cellmid take longer than expected to make it into the clinic;
  - **Clinical risk**. There is the risk that the anti-midkine antibody fails to register responses in the first Phase I/II study in cancer; and
  - **Funding risk**. Even though Cellmid has some near-term revenue streams, there will likely be further capital required if the full potential of the midkine programmes are to be realised.

Major shareholders

- Currently there are no substantial shareholders in Cellmid.

[78] Sydney, Australia, privately held, www.istl.com.au. Immune System Therapeutics is working on a multiple myeloma antibody.
[79] Now the world's 27th largest pharma company – source: Pharmaceutical Executive.
[80] Mesoblast (Melbourne, Australia, ASX: MSB, www.mesoblast.com) is the world's leader in stem cell drug development.
[81] Redwood City, Ca., Nasdaq: PMBD, www. primabiomed.com.au.

Appendix I – A Cellmid glossary

Acute Myocardial Infarction (AMI) – The medical term for a heart attack, that is, a blockage of blood supply to the heart muscle (the myocardium).

Advangen – A Japanese company that had developed hair regrowth products which Cellmid is now commercialising.

Antibody – Immune system proteins that can bind to an antigen and help to neutralise the potentially harmful effects of the cells carrying the antigen.

Antisense – Methods for blocking the message – the 'sense'- of the DNA behind the creation of a protein.

Alopecia – Complete or partial hair loss.

Angiogenesis – The process underlying the formation of new blood vessels, including the blood vessels which feed tumours.

Antigen – The 'bad guy' substance that stimulates the immune system to respond to the perceived threat. It is the protein to which antibodies bind.

Apoptosis – 'Programmed' cell death, that is, cell death that is naturally-occurring. Cancer cells tend to avoid apoptosis.

Aptamer – A nucleic acid molecule that binds to a specific target molecule.

Atherosclerosis – The clogging or hardening of blood vessels caused by plaques of fatty deposits, usually cholesterol.

Autoimmune disease – Disease in which the immune system is attacking 'self' antigens rather than 'non-self antigens'. Rheumatoid Arthritis is an autoimmune disease.

Big Pharma – A collective term referring to the world's largest pharmaceutical companies such as Eli Lilly, J&J, Merck & Co., Novartis and Pfizer.

Biomarker – A natural substance used as an indicator of a biological state, especially to detect the presence or severity of disease.

Blockbuster – A pharmaceutical drug with more than US$1bn in annual sales.

Cardiac remodelling – Changes in cardiac tissue as a result of heart failure.

COPD – Short for Chronic Obstructive Pulmonary Disease, COPD is an umbrella term for a number of progressive, long-term lung conditions characterised by shortness of breath due to reduced airflow through the airways.

Diabetic nephropathy – Kidney damage resulting from diabetes, which can often lead to kidney failure.

Dose escalation – A situation in a drug trial where an increasing dose is administered in order to find an optimal dose.

ELISA – Short for Enzyme-Linked ImmunoSorbent Assay, a test method for antigens in blood that involves the detection of a linked enzyme. ELISAs represent a way of screening many samples at once, through the use of trays containing multiple sample wells.

évolis – Cellmid's hair regrowth product that works through inhibition of FGF-5.

FDA – The Food and Drug Administration, the American government body which regulates the pharmaceutical industry and from whom approval must be received before a drug can be marketed in the US.

FGF-5 – A growth factor that regulates hair growth. Cellmid's hair regrowth products work by inhibition of FGF-5.

Glomerular sclerosis – A condition in which the glomeruli – the network of blood-filtering capillaries in the kidney – become scarred and gradually lose their function.

Haemopoietic stem cells – Stem cells that help build the body's blood supply.

Heart failure – A condition where the heart is unable to pump adequate amounts of blood around the body. Heart failure often follows on from an Acute Myocardial Infarction.

Heparin – A compound occurring in the liver and other tissues which inhibits blood coagulation. Natural and synthetic heparin are used as anti-clotting drugs.

Infarct – A localised area of dead tissue resulting from failure of blood supply.

In vitro – Latin for 'in glass', referring to data obtained through testing in a test tube.

Ischemia – Lack of adequate blood flow to support the normal functioning of a tissue.

Knockout mice – Mice that have been bred to lack a particular gene, so that the effect of that loss can be studied.

Macrophages – White blood cells involved in the immune system's response to infection. Macrophages are not found in the bloodstream but at locations where body organs interface with the environment or the bloodstream.

Midkine (mk) – A small heparin-binding growth factor protein that is important in embryonic development and, while not detectable in healthy adults, is highly expressed in cancer and autoimmune disorders.

Monoclonal antibodies – Antibodies cloned from a particular cell-making antibody that is highly specific for a particular antigen. Monoclonal antibodies are increasingly used as drugs**.**

Neuroblastoma –A cancer of the neuroblast nerve cell precursors, occurring most often in infants and young children. Neuroblastoma is rare, with only ~700 new cases in the US each year.

Neutrophil – A white blood cell vital for immune system function. Neutrophils work by ingesting foreign cells.

Non-small-cell lung cancer (NSCLC) – One of two main types of lung cancer, the other being small-cell lung carcinoma. Non-small cell lung cancer is easier to surgically remove.

Oligonucleotides – Short strings of nucleotides, that is, DNA or RNA 'letters' from the genetic alphabet.

Oncogenic – Capable of causing cancer.

Open label – A clinical trial in which both patients and doctors know what treatment is being administered.

PTCA – Short for Percutaneous Transluminal Coronary Angioplasty, a surgical procedure to repair a damaged blood vessel or unblock a coronary artery. In PTCA a balloon is inserted via a catheter into the vessel and then expanded.

pg/mL – Picograms per millilitre, a measurement of the serum concentration of rarely-occurring proteins. A picogram is a trillionth of a gram.

Phase – A stage of the clinical trialling process for a drug candidate. Phase I tests for safety. Phase II tests for efficacy in a small sample. Phase III tests for efficacy in a large sample.

Regulatory T cells – T cells which turn down an immune response.

Reperfusion – The return of blood supply to tissue after a period of ischemia.

Restenosis – A re-narrowing or blockage of an artery at a site where angioplasty was previously done. An angioplasty is a procedure to open clogged arteries, performed after a heart attack. Restenosis often follows administration of a stent.

Sepsis – Serious and potentially life-threatening inflammation caused by severe infection.

Serum – Blood plasma from which the clotting proteins have been removed. Plasma is the clear fraction of the blood. The serum concentration of a protein relative to its normal level can be indicative of disease.

Sjögren's syndrome – An autoimmune disorder in which the white blood cells attack the moisture-producing glands, causing decreased production of saliva and tears. Sjögren's syndrome may affect 3-4% of the adult population[82].

Trispecific – An antibody drug that can hit three different targets.

Wild-type – The natural version of a particular gene, protein, or strain.

Xenograft – An animal model of cancer in which a human tumour is grafted onto a mouse without a functioning immune system, so that the tumour will stay in place.

[82] See Br J Rheumatol. 1998 Oct;37(10):1069-76.

Appendix II – Key patents

- **Novel use of mk family as hematopoietic factor**, WO/1998/001151, Exp. Jan-2017[83]. This patent application covers the use of midkine as a growth factor in the expansion of hematopoietic stem cells for use in bone marrow transplant.
- **Drugs containing as the active ingredient midkine or inhibitors thereof**, WO/1999/003493, Exp. Jan-2018[84]. This patent application covers the therapeutic uses that can be made of midkine as a promoter of neutrophilic inflammation.
- **Preventives or remedies for ischemic diseases**, WO/1999/016463, Exp. Jan-2018[85]. This patent application covers the use of midkine protein in treating heart attack and stroke.
- **Mass secretion/expression system of true mk family protein**, WO/2000/009718, Exp. Jan-2019[86]. This patent application covers a yeast-based expression system for producing midkine protein.
- **Pharmaceutical compositions for the prevention and treatment of atherosclerosis and restenosis after PTCA**, WO/2000/010608, Exp. Jan-2019[87]. This patent application covers midkine inhibitors used to prevent restenosis following heart bypass surgery.
- **Early cancer tumour marker**, WO/2001/020333, Exp. Jan-2020[88]. This patent application covers the use of midkine in cancer diagnostics.
- **Preventive for adhesion following abdominal surgery**, WO/2004/078210, Exp. Jan-2024[89]. This patent application covers the use of midkine inhibitors in preventing surgical adhesions by blunting the associated inflammation.
- **Hair growth stimulant composition**, WO/2005/034894, Exp. Jan-2024[90]. This patent application covers the use of FGF-5 inhibitors in promoting hair regrowth.
- **Composition for treating or preventing myocardial disorder or heart failure**, WO/2006/062087, Exp. Jan-2025[91]. This patent application covers the use of midkine protein in treating heart attack and thereby preventing heart failure.
- **Pharmaceutical composition for vascular occlusive disease**, WO/2006/126600, Exp. Jan-2026[92]. This patent application covers the use of midkine to treat various disease conditions in which blood vessels are in danger of closing.
- **Method for treatment or prevention of disease associated with functional disorder of regulatory T cell**, WO/2007/055378, Exp. Jan-2026[93]. This patent application covers the use of midkine antagonists in treating Multiple Sclerosis.
- **Therapeutic agent for occlusive peripheral vascular disease, and use thereof**, WO/2008/047904 , Exp. Jan-2027. This patent application covers the use of midkine in promoting the new blood vessel growth which would treat peripheral artery disease.
- **Antibody recognising C-domain of midkine**, WO/2008/059616, Exp. Jan-2027[94]. This patent application covers antibodies to one of the two midkine domains.
- **Nitric oxide synthase activator**, WO/2008/129851, Exp. Jan-2028[95]. This patent application covers the use of midkine in vasodilation, that is, expansion of blood vessels through activation of nitric oxide synthase.
- **Method of treatment or prevention of hair loss or for the enhancement of hair growth**, WO/2011/103624, Exp. Jan-2031[96]. This patent application covers the use of midkine as a promoter of hair growth.

[83] This patent application has been granted in the US as Patents No. 6,383,480 (May 2002) and 6,939,669 (September 2005) and in Europe as EP 0 937 461 (July 2005).
[84] This patent application has been granted in the US as Patent No. 7,390,491 (June 2008) and in Europe as EP 0 998 941 (June 2006).
[85] This patent application has been granted in Europe as EP 1 057 489 (January 2007).
[86] This patent application has been granted in the US as Patent No. 6,867,037 (March 2005).
[87] This patent application has been granted in the US as Patent Nos. 7,309,695 (December 2007) and 7,820,160 (October 2010) and in Europe as EP 1 108 436 (August 2009).
[88] This patent application has been granted in the US as Patent No. 7,090,983 (August 2006) and in Europe as EP 1 215 500 (July 2008)
[89] This patent application has been granted in the US as Patent No. 8,221,758 (July 2012).
[90] This patent application was made by Advangen.
[91] This patent application has been granted in Europe as EP 1 832 296 (August 2009).
[92] This patent application has been granted in Europe as EP 1 900 380 (March 2013).
[93] This patent application has been granted in the US as Patent No. 8,128,934 (March 2012).
[94] This patent application has been granted in Europe as EP 2 088 159 (March 2014).
[95] This patent application has been granted in the US as Patent No. 8,288,343 (October 2012).
[96] This patent application was made by Advangen.

- **Antibody recognising N-domain of midkine**, WO/2012/122590, Exp. Jan-2032. This patent application covers antibodies to the other midkine domains, WO/2008/059616 above having covered the C-domain.
- **Biochemical evaluation method**, WO/2013/105417, Exp. Jan-33[97]. This patent application covers a method of detecting whether or not a growth factor is having the desired effect on cell growth. It involves culturing dermal papilla cells in the presence of the growth factor and measuring the level of alkaline phosphatase activity.

Appendix III – Comparable companies

FIG.1: CELLMID COMPARABLES[98]

Name	Location	Code	Market cap (USDm)	Web site
Sorrento Therapeutics	San Diego, Ca.	Nasdaq: SRNE	112.6	www.sorrentotherapeutics.com
Epigenomics	Berlin, Germany	Xetra: ECX	97.8	www.epigenomics.com
LipoScience	Raleigh, NC	Nasdaq: LPDX	80.5	www.liposcience.com
Vermillion	Austin, Tx.	Nasdaq: VRML	55.1	www.vermillion.com
Immune Pharmaceuticals	Herzliya, Israel	OTCQX: IMNP	55.1	www.immunepharmaceuticals.com
Lpath	San Diego, Ca.	Nasdaq: LPTN	49.5	www.lpath.com
Bioinvent	Lund, Sweden	Nasdaq OMX Stockholm:	43.5	www.bioinvent.com
Trillium Therapeutics	Toronto, On.	TSX: TR	37.2	www.trilliumtherapeutics.com
Response Genetics	Los Angeles, Ca.	Nasdaq: RGDX	21.3	www.responsegenetics.com

Source: Company data

- **Bioinvent**. This cancer antibody drug developer, built on an antibody screening tool called F.I.R.S.T, is in Phase II with BI-505, an antibody specific for the adhesion protein ICAM-1, overexpressed in several tumours but not widely expressed in normal tissue. The initial indication for BI-505 is in multiple myeloma.
- **Epigenomics**. This company, built on methods to detect DNA methylation, develops cancer-specific molecular diagnostics. The company's lead product, Epi proColon, a blood test for the early detection of colorectal cancer, is currently marketed in Europe.
- **Immune Pharmaceuticals**. This company's lead product is bertilimumab, a Phase II antibody for ulcerative colitis and Crohn's Disease. The company is also working on antibody nanoparticle conjugates for the targeted delivery of chemotherapeutics as well as a couple of small molecules in cancer and neuropathic pain.
- **LipoScience**. This company's technology enables lipoproteins and other and small molecule metabolites relevant to disease to be identified from a blood sample using nuclear magnetic resonance. The company's first FDA-approved product was the NMR LipoProfile for quantifying particles of LDL, that is, 'bad' cholesterol.
- **Lpath**. This company develops antibodies that target bioactive lipids. The company's lead candidate is sonepcizumab, which targets S1P and is in Phase II in wet AMD. An S1P antibody is useful in various disease conditions including cancer, MS and ulcerative colitis. The wet AMD indication was optioned to Pfizer in December 2010 for US$14m upfront. Pfizer has since been seeking new assignees for this option.
- **Response Genetics**. This company develops cancer molecular diagnostics using technology to extract genetic information from tumour samples. The company currently generates revenue from analytical pharmacogenomic testing services of clinical trial specimens. The company's ResponseDX Biomarker tests are used to test for lung, colon, gastric, melanoma, breast and thyroid cancers.
- **Sorrento Therapeutics**. This cancer drug developer has Cynviloq, a nanoparticle formulation of paclitaxel, as its lead compound in late stage clinicals. Resiniferatoxin, a non-opiate pain therapeutic for cancer pain, is in mid-stage clinical development. Various antibody drugs are pre-clinical.
- **Trillium Therapeutics**. This company is focused on cancer stem cell therapies. Its most promising cancer products, both preclinical, are an antibody-like fusion protein to CD47,

[97] This patent application was made by Advangen.
[98] 21 November 2014 close on Nasdaq and elsewhere.

and an antibody to CD200. The CD47 product is targeting cancer stem cells in Acute Myeloid Leukaemia. The CD200 product hits a molecule overexpressed by many tumours.

- **Vermillion**. This company develops diagnostics specific to gynaecologic cancers – cervical, ovarian, uterine and vaginal/ vulvar – as well as women's health. The company's main product is its OVA1 test, which measures five proteins relevant in ovarian cancer.

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