NDF RESEARCH

Providing independent research coverage of
ASX-listed Life Science companies

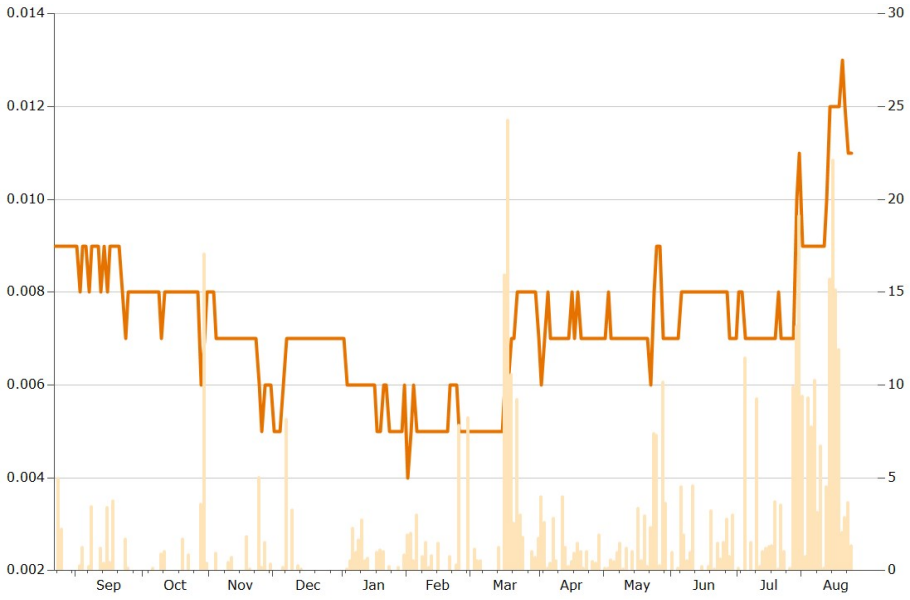
Dimerix (ASX: DXB)

Initiation of Coverage – Thursday 25 August 2016

Hitting the GPCR spot

Dimerix is a Melbourne and Perth-based drug discovery company being built around new ways to identify G Protein-Coupled Receptors, the target of a significant number of present and former blockbuster drugs. Dimerix's Receptor-Heteromer Investigation Technology (Receptor-HIT) allows druggable GPCR combinations to be identified. Dimerix's lead DMX-200 candidate, a combination of two existing drugs, irbesartan and propagermanium, is now in a Phase II study in patients with proteinuria, which is symptomatic of a range of kidney problems. Following recent guidance from the FDA, Dimerix is now making plans to take DMX-200 into a pivotal study in Focal Segmental Glomerulosclerosis, an Orphan kidney disease. We value Dimerix at 2.4 cents per share base case and 5.9 cents per share optimistic case. Our target price of 4.0 cents per share sits at the midpoint of our DCF range.

Rating	Risk	Current price	Target price
Buy	Speculative	$0.010	$0.04



Stock details

Daily Turnover: ~A$36,000
Market Cap: A$14.7m
Shares Issued: 1,473.6m
52-Week High: $0.013
52-Week Low: $0.005

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Please note: Please refer below for risks related to Dimerix as well our General Advice Warning, disclaimer and full disclosures. Also please be aware that the investment opinion in this report is current as at the date of publication but that the circumstances of the company may change over time, which may in turn affect our investment opinion.

About NDF Research

NDF is an independent equity research firm based in Sydney, Australia. It focuses on Life Science companies that are publicly traded on the Australian Securities Exchange (ASX). This Exchange hosts one of the world's premier equity markets for biotech and medical device companies, and is home to world-beating companies such as CSL and ResMed and emerging pioneers such as Mesoblast and Impedimed.

NDF's Founder and Senior Analyst, Stuart Roberts, has been involved in Life Sciences since 2002 as a sell-side analyst as well as an executive of two ASX-listed immuno-oncology drug developers.

NDF believes that ASX-listed companies have been largely overlooked in the global Life Sciences boom that began in late 2008, partly because of insufficient quality research. NDF's goal is to provide such research, and introduce investors around the world to potential future billion dollar companies from 'Down Under'.

To learn more about the Life Sciences sector on the ASX and our firm, please visit ndfresearch.com.

Ferry at the end of a rainbow on Sydney Harbour, August 2014

In this report

Financial summary

Code	DXB
Analyst	Stuart Roberts
Date	25 August, 2016
Share price	$0.0100
Market capitalisation	$15m
Year end	30 June

Rating	BUY
Price target	$0.040
Upside/downside	300.0%
Valuation	$0.024 / $0.059
Valuation method	Probability-weighted DCF
Risk	Speculative

PROFIT AND LOSS (A$m)

Y/e June 30 (A$m)	FY14A	FY15A	FY16E	FY17E	FY18E
Revenue	0.1	0.0	0.0	0.0	24.2
EBITDA	**-0.6**	**-0.7**	**-5.5**	**-8.4**	**15.7**
D&A	0.0	0.0	0.0	0.0	0.0
EBIT	**-0.6**	**-0.7**	**-5.5**	**-8.4**	**15.7**
Net interest	0.0	0.0	0.0	0.0	0.0
Pre-tax profit	**-0.5**	**-0.7**	**-5.5**	**-8.4**	**15.7**
Tax	0.0	0.0	0.0	0.0	0.0
NPAT	-0.5	-0.7	-5.5	-8.4	15.7
Minority interests	0.0	0.0	0.0	0.0	0.0
Net profit after minorities	-0.5	-0.7	-5.5	-8.4	15.7

BALANCE SHEET (A$m)

Y/e June 30	FY14A	FY15A	FY16E	FY17E	FY18E
Cash	1.2	2.9	2.0	4.7	19.7
Current receivables	0.0	0.0	0.2	0.2	1.1
Inventories	0.0	0.0	0.0	0.0	0.9
Other current assets	0.0	0.0	0.0	0.0	0.0
Current assets	**1.2**	**3.0**	**2.3**	**4.9**	**21.8**
PPE	0.0	0.0	0.0	0.1	0.1
Intangible assets	0.0	0.0	0.0	0.0	0.0
Other non-current assets	0.0	0.0	0.0	0.0	0.0
Non-current assets	0.0	0.0	0.0	0.1	0.1
Total assets	1.2	3.0	2.3	5.0	21.8
Payables	0.0	0.2	0.1	0.1	0.7
Debt	0.0	0.0	0.0	0.0	0.0
Other liabilities	0.0	0.0	0.0	0.0	0.0
Total liabilities	0.0	0.2	0.1	0.1	0.7
Shareholders' equity	1.2	2.8	2.2	4.9	21.1
Minorities	0.0	0.0	0.0	0.0	0.0
Total shareholders funds	**1.2**	**2.8**	**2.2**	**4.9**	**21.1**
Total funds employed	**1.2**	**3.0**	**2.3**	**5.0**	**21.8**
W/A shares on issue	172	205	782	2,458	2,547

CASH FLOW (A$m)

Y/e June 30	FY14A	FY15A	FY16E	FY17E	FY18E
NPAT plus discontinued ops.	-0.5	-0.7	-5.5	-8.4	15.7
Non-cash items	0.0	0.0	3.3	0.4	0.4
Working capital	0.0	0.1	0.8	0.0	-1.2
Other operating cash flow	0.0	0.0	0.0	0.0	0.0
Operating cashflow	**-0.6**	**-0.5**	**-1.3**	**-8.0**	**14.9**
Capex	0.0	0.0	0.5	0.0	0.0
Investments	0.6	-0.1	0.0	0.0	0.0
Other investing cash flow	0.0	0.0	0.0	0.0	0.0
Investing cashflow	**0.6**	**-0.1**	**0.5**	**0.0**	**0.0**
Change in borrowings	0.0	0.0	0.0	0.0	0.0
Equity raised	0.0	2.4	0.0	10.7	0.1
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	**0.0**	**2.4**	**0.0**	**10.7**	**0.1**
Net change in cash	**0.0**	**1.7**	**-0.9**	**2.7**	**15.0**
Cash at end of period	1.2	2.9	2.0	4.7	19.7

EARNINGS (A$m)

Y/e June 30	FY14A	FY15A	FY16E	FY17E	FY18E
Net profit ($m)	-0.5	-0.7	-5.5	-8.4	15.7
EPS (c)	-0.3	-0.3	-0.7	-0.3	0.6
EPS growth (%)	N/A	N/A	N/A	N/A	N/A
P/E ratio (x)	-3.3	-3.0	-1.4	-2.9	1.6
CFPS (c)	-0.3	-0.3	-0.2	-0.3	0.6
Price/CF (x)	-3.0	-3.7	-5.8	-3.1	1.7
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	-23.8	-16.6	-2.3	-1.2	-0.3
EV/EBIT	-23.8	-16.6	-2.3	-1.2	-0.3

PROFITABILITY RATIOS

Y/e June 30	FY14A	FY15A	FY16E	FY17E	FY18E
EBITDA/revenue (%)	N/A	N/A	N/A	N/A	65.0%
EBIT/revenue (%)	N/A	N/A	N/A	N/A	64.9%
Return on assets (%)	-43.5%	-22.9%	-238.5%	-167.8%	72.0%
Return on equity (%)	-44.8%	-24.5%	-247.1%	-170.5%	74.4%
Return on funds empl'd (%)	-44.8%	-24.5%	-247.1%	-170.5%	74.4%
Dividend cover (x)	N/A	N/A	N/A	N/A	0%
Effective tax rate (%)	0.0%	0.0%	0.0%	0.0%	0.0%

LIQUIDITY AND LEVERAGE RATIOS

Y/e June 30	FY14A	FY15A	FY16E	FY17E	FY18E
Net debt/(cash) ($m)	-1	-3	-2	-5	-20
Net debt/equity (%)	-101.7%	-105.5%	-92.4%	-96.0%	-93.1%
Net interest cover (x)	N/A	N/A	N/A	N/A	N/A
Current ratio (x)	35.7	15.5	28.3	61.7	31.2

INTERIMS

Y/e June 30 ($m)	1H15A	2H15A	1H16A	2H16F	1H17F
Revenue	0.0	0.0	0.0	0.0	0.0
EBITDA	**-0.3**	**-0.4**	**-4.8**	**-0.7**	**-4.2**
D&A	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
EBIT	**-0.3**	**-0.4**	**-4.8**	**-0.7**	**-4.2**
Net interest	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Pre-tax profit	-0.3	-0.4	-4.8	-0.7	-4.2
Tax	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
NPAT	-0.3	-0.4	-4.8	-0.7	-4.2
Minority interests	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Net profit after minorities	-0.3	-0.4	-4.8	-0.7	-4.2

VALUATION

	Base	Optimistic
Value of Dimerix technology	54.1	144.7
Value of tax losses	2.8	2.8
Corporate overhead	-7.2	-7.2
Cash now (A$m)	2.0	2.0
Cash to be raised (A$m)	10.0	10.0
Option exercises (A$m)	1.4	1.4
Total value (A$m)	63.0	153.6
Total diluted shares (million)	2621.9	2621.9
Value per share	$0.024	$0.059
Valuation midpoint	$0.042	
Share price now (A$ per share)	$0.010	
Upside to midpoint	315.0%	

Introducing Dimerix (ASX: DXB)

- **Who is Dimerix?** Dimerix is a Melbourne and Perth-based drug discovery company being built around new ways to identify G Protein-Coupled Receptors, the target of a significant number of the world's best-selling drugs. Dimerix's Receptor-Heteromer Investigation Technology (Receptor-HIT) allows druggable GPCR combinations to be identified. Dimerix's lead DMX-200 candidate, a combination of two safe and approved drugs, irbesartan and propagermanium, is now in a Phase II study in patients with proteinuria, which is symptomatic of a range of kidney problems. Following recent guidance for the FDA, Dimerix is now making plans to take DMX-200 into a pivotal study in Focal Segmental Glomerulosclerosis, an Orphan kidney disease.
- **What are G Protein-Coupled Receptors and why are they commonly the target of blockbuster drugs?** A great many cellular functions are controlled by molecular signalling pathways that begin with a cell surface receptor and the associated natural binding partner of that receptor, called its 'ligand'. When these two join together, the result is a change in the shape of the interior part of the receptor, which allows it to activate another signalling molecule inside the cell. This signalling molecule in turn passes the signal to other molecules in a cascade of signalling activity until the required changes in the cell's behaviour or characteristics are effected. G Protein-Coupled Receptors, so-called because they pass the signals they receive onto intracellular 'G proteins', are amongst the most important of these cell surface receptors, because they seem to have a role in the whole of physiology. They are present in just about every organ system, and as a result have been considered as targets for a wide range of disease areas including heart disease, cancer, diabetes, inflammation and CNS disorders. This ubiquity explains why the Royal Swedish Academy of Sciences, in awarding the 2012 Nobel Prize for Chemistry to the American scientists Robert Lefkowitz and Brian Kobilka for their work on GPCRs, commented that '*about half of all medications achieve their effect through G protein–coupled receptors*'[1].

ABOUT HALF OF ALL MEDICATIONS ACHIEVE THEIR EFFECT THROUGH G PROTEIN-COUPLED RECEPTORS

- **How is Dimerix a player in the G Protein-Coupled Receptor space?** Dimerix is being built on a platform called Receptor-Heteromer Investigation Technology (Receptor-HIT) that allows druggable 'dimers' of GPCRs, known as GPCR heteromers, to be identified. Until recently the pharma industry had more or less been interested in drugging only individual GPCRs. However, it is now becoming apparent that many different GPCRs complex together, with these heteromers having a different functionality to the constituent GPCRs. This opens up the potential for many new GPCR targets, and may also explain some unexpected effects of drugs thought to act on a single receptor. Since Dimerix's platform is cell-based and real-time, it arguably has the world's most efficient way of identifying GPCR heteromers, and is therefore a corporate 'thought leader' in this new field. Importantly, Dimerix owns granted patents in major jurisdictions protecting this assay.
- **What new drugs has Dimerix discovered with its Receptor-HIT platform?** Dimerix's lead candidate, DMX-200, is the former blockbuster blood pressure drug irbesartan plus a less-well-known anti-inflammatory drug called propagermanium that is approved in Japan for the treatment of Hepatitis B infection. DMX-200 originated from the discovery by Dimerix's scientists that a GPCR called AT1R, which

[1] Source: Royal Swedish Academy of Sciences press release dated 10 October 2012.

is targeted by irbesartan, forms a GPCR heteromer with CCR2, which is the target of propagermanium, and that this GPCR heteromer is highly relevant in kidney disease. To test its hypothesis that DMX-200 can treat kidney disease, Dimerix has taken the product into a Phase II study in patients with proteinuria, that is, excessive protein in the urine, which is symptomatic of a range of kidney problems. Dimerix's *in vivo* data suggests that DMX-200 can lower proteinuria by at least 50%, which is considered a clinically meaningful outcome in kidney disorders such as nephrotic syndrome, which is characterised by damage to the glomeruli that provide part of the kidney's blood filtering function. Patients with nephrotic syndrome and Chronic Kidney Disease are already routinely treated with irbesartan. Dimerix is developing an extended-release formulation of propagermanium that will be additive to irbesartan. Dimerix's Phase II study in proteinuria patients is currently in the dose finding stage, with a second stage expected to be run at the optimal dose. After this, following on from guidance obtained from the FDA in June 2016, the company intends to run a single pivotal study in Focal Segmental Glomerulosclerosis (FSGS) a rare nephrotic syndrome disorder for which Dimerix has obtained Orphan Drug Status from the FDA. Dimerix's original irbesartan-plus-propagermanium product has patent protection until 2032 with further patent life available once the extended-release formulation of propagermanium is completed.

- **What is the upside for Dimerix with DMX-200?** With DMX-200 there is potential for Dimerix to quickly become a Phase III drug developer by 2019. The actual drug could be game-changing in kidney disease given the lack of new drugs in this space and the fact that ~12% of the US adult population has some sort of Chronic Kidney Disease. Consequently, there is potential for DMX-200 to branch out from FSGS to other larger-market indications.
- **What is the upside for Dimerix with its Receptor-HIT platform?** Other than DMX-200 we see two main upsides from the platform. Dimerix is currently working on a pipeline of GPCR heteromer-targeting candidates for nonalcoholic steatohepatitis (NASH), diabetic retinopathy, cancer fatigue and multiple sclerosis. In addition to this, it's not unreasonable to expect Big Pharma to be interested in the platform for its own GPCR drug discovery efforts, particular after two GPCR platform companies, Receptos and Heptares, were acquired in 2015. Two 'Top 10' pharma companies, along with Takeda[2], Japan's largest pharmaceutical company, have in the past used Receptor-HIT in paid collaborations with Dimerix scientists.
- **If Dimerix is this good, how come its market capitalisation is only A$14.7m?** Dimerix was taken public on the Australian Securities Exchange in mid-2015 through a backdoor-listing[3] after raising A$1.6m at 1.0 cent per share. The stock has since traded at between 0.5 cents and 1.3 cent per share. We think that Dimerix currently has a low market capitalisation relative to its potential for two reasons. Firstly, there has been no clinical data related to the performance of DMX-200 in patients with proteinuria. Secondly, the company until recently could be regarded as early stage since this is DMX-200's first time in the clinic. However, we think that, with interim data from the Phase II study imminent, and FDA guidance now

TWO TOP-TEN PHARMA COMPANIES HAVE IN THE PAST USED DIMERIX'S PLATFORM

[2] Osaka, Japan, TSE: 4502, www.takeda.com. Takeda was the world's 18th largest pharma company in 2015 (source Pharmaceutical Executive magazine).
[3] 'Backdoor listing' is an Australian term for what is known in US equity markets as a 'Reverse Takeover'. Dimerix, originally a spin-out from the Western Australian Institute for Medical Research, was merged into a defunct biotech company called Sun Biomedical (ASX: SBN) that had been working on saliva-based drug tests and asthma diagnostics and therapeutics. Sun Biomedical acquired Dimerix for 750 million shares plus three blocks of performance shares, each worth 75 million ordinary shares on conversion. The first block converted to ordinary shares in February 2016 when Dimerix received Notice of Allowance for what became US patent 9,314,450. The second block was converted in April 2016 when Dimerix requested a pre-IND meeting with the FDA. The third block will convert when Dimerix gains ethics approval for a clinical trial in a second indication beyond FSGS.

available for a pivotal study in FSGS, sentiment towards Dimerix will shift towards regarding the company as more of a late stage opportunity.

Ten reasons to consider Dimerix

- **G Protein Coupled Receptors are important to modern medicine**. With a significant number of past and present blockbusters targeting GPCRs, Big Pharma is highly aware of the importance of this class of receptor to the future of medicine. Consequently, any company like Dimerix with capability for finding new GPCR drug targets, and novel pharmacology related to those targets, is likely to attract attention.
- **GPCR drug discovery platforms have the potential to create significant value**. The sale of Heptares to Sosei for US$180m upfront and US$220m in milestones, and of Receptos to Celgene for a massive US$7.2bn in cash, show the value which the pharma industry places on the ability to easily find and characterise new GPCR drug targets.
- **GPCR heteromers as drugs targets are finally coming into their own**. The realisation that GPCRs form heteromers, and that these heteromers behave differently from their constituent GPCRs, has opened up a new field of GPCR research which Dimerix is leading because its platform allows GPCR heteromers to be discovered and their pharmacology interrogated in cells and in real-time.
- **DMX-200 is a great lead candidate in kidney disease**. The *in vivo* data has suggested that DMX-200, where one safe and approved drug is added to another, is potentially a new treatment for nephrotic syndrome and Chronic Kidney Disease. Interim data from the initial Phase II dose finding study will release before the end of 2016.
- **The potential payoff in kidney disease is strong**. In the US around 26% of the population over the age of 60 has Stage 3 or worse Chronic Kidney Disease[4] with at least 700,000 people suffering End-Stage Renal Disease. This high prevalence suggests a strong market opportunity for any new drugs relevant in kidney disease.
- **Dimerix has received what it considers to be favourable regulatory guidance**. Dimerix reported to the market in July 2016 that it had been encouraged by its pre-IND meeting with the FDA, where the Agency had indicated that only a small pivotal study with proteinuria reduction as a primary endpoint would, subject to clinical success, potentially be sufficient for approval in Focal Segmental Glomerulosclerosis (FSGS). The Agency has also indicated that it would treat DMX-200 as adjunct therapy, with propagermanium adjuctive to standard-of-care irbesartan. This removes concerns about having to prove the safety of combination therapy.
- **Dimerix is an Orphan Drug company**. With the company having gained Orphan Drug status for DMX-200 in FSGS in December 2015, Dimerix is now set to enjoy the benefits of being an Orphan Drug developer in terms of speed to market and potentially favourable pricing in its early indications.

CELGENE BOUGHT THE GPCR PLATFORM COMPANY RECEPTOS FOR US$7.2BN

[4] Source: NHANES 2001-2008 data.

- **Dimerix is building a pipeline from its GPCR platform,** with potential candidates for pre-clinical development in nonalcoholic steatohepatitis (NASH), diabetic retinopathy, cancer fatigue and multiple sclerosis. We see any developments in the pipeline, such as was recently reported for the NASH candidate, as strengthening sentiment towards Dimerix as an identifier of druggable GPCR targets.
- **Dimerix has a solid management team**. Dr James Williams, Executive Chairman of Dimerix, brings to the company a track record of success in Life Sciences ventures that has included successful product launches at Resonance Health and Argus Biomedical and the sale of iCeutica to Iroko Pharmaceutical. Backing Williams is a board that includes Dr Sonia Poli, formerly of the Swiss drug developer Addex, a company which has a strong GPCR focus.
- **Dimerix is trading below its potential.** We value Dimerix at 2.4 cents per share base case and 5.9 cents per share optimistic case. Our target price of 4.0 cents per share sits at the midpoint of our DCF range. We see Dimerix being re-rated by the market as interim Phase II data becomes available for DMX-200 in patients with proteinuria and as the Dimerix pipeline develops further.

Big Pharma wants G Protein-Coupled Receptors

Dimerix is a drug discovery company whose main technology platform allows for the identification of new G Protein-Coupled Receptor (GPCR) drug targets. Specifically, the platform can identify druggable GPCR complexes known as GPCR heteromers. We think there are five reasons why Dimerix's platform can become highly valuable for shareholders over time.

1. A significant number of past and present blockbuster drugs work by targeting G Protein-Coupled Receptors, making for strong pharma interest in new GPCR targets;
2. It is now possible to properly characterise GPCRs, thanks to the first technology platforms that were set up less than a decade ago to detect new GPCR targets;
3. The early GPCR platforms sold for very high prices in 2015 – Heptares to the Japanese pharma company Sosei for US$400m in total deal value; and Receptos to Celgene for a massive US$7.2bn in cash;
4. Even with the improved GPCR discovery technology of recent years, as developed by Heptares, Receptos and others, most individual GPCRs in the human genome have yet to be drugged, meaning that the field is far from exhausted;
5. GPCR heteromers – basically combinations of GPCRs – have only recently been recognised as an important class of new GPCR target, and Dimerix is widely regarded as pioneering this new discovery effort.

MOST GPCRS HAVE YET TO BE DRUGGED

A significant number of past and present blockbuster drugs target GPCRs. At any one time a significant percentage of the global pharmaceutical industry's revenue will come from drugs that target GPCRs. Omeros, a US drug discovery company with a focus on GPCRs, asserts that 'nearly 40% of all drugs sold worldwide target GPCRs'[5] while one 2006 analysis suggested that 27% of all drugs targeted 'Class I' GPCRs[6]. According to Heptares, six of the top ten and 60 of the top 200 best-selling drugs in the US in 2010 targeted GPCRs[7]. Figure 1 lists a number of recent GPCR-targeting blockbusters. The developers of these drugs, which originated in most cases in the 1980s and 1990s, identified them on the basis of functional activity observed in various assays with little regard for whether or not the relevant target was a GPCR[8]. Indeed, until the 2000s it was just about impossible to do rational drug design on GPCRs, as we'll see below. However, the success of GPCR-modulating agents in such diverse settings convinced the pharmaceutical industry that GPCRs were a very valuable field in which to explore, particularly since there were around 300-400 of them in the human genome that were pharmaceutically interesting[9] but only around 50-60 of those had become the target of approved drugs. This strong interest by pharma led, between 2007 and 2009, to the emergence of the first drug discovery platforms that allowed the GPCR field to be systematically explored.

Figure 1 Some recent blockbuster drugs that work by targeting GPCRs

Brand name	Generic name	Target	Main indications	Maker	FDA approval	Peak sales (US$bn)
Plavix	clopidogrel	platelet P2Y12 receptor	Prevention of blood clots	Bristol-Myers Squibb	Nov-97	$16.8bn (2011)
Advair	fluticasone propionate and salmeterol	glucocorticoid receptor (GR, fluticasone), β2-adrenoceptor (ADRB2, salmeterol)	Asthma and COPD	GlaxoSmithKline	Aug-00	$8.9bn (2013)
Diovan	valsartan	angiotensin II type I receptor (At1)	Hypertension	Novartis	Jan-97	$6.1bn (2010)
Seroquel	quetiapine	serotonin 5-HT2 and dopamine D2 receptors	Bipolar disorder	AstraZeneca	Sep-97	$5.8bn (2011)
Spiriva	tiotropium bromide	Muscarinic acetylcholine receptors (mAChRs)	COPD	Boehringer Ingelheim	Jan-04	$5.5bn (2014)
Singulair	montelukast	cysteinyl leukotriene receptor 1 (CysLT1)	Asthma	Merck & Co.	Feb-98	$5.5bn (2011)
Zyprexa	olanzapine	serotonin 5-HT2 and dopamine D2 receptors	Bipolar disorder and schizophrenia	Eli Lilly	Sep-96	$5bn (2010)
OxyContin	oxycodone	μ-opioid receptor (MOR)	Chronic pain	Purdue Pharma	Dec-95	$3.1bn (2010)
Abilify	aripiprazole	dopamine D2 receptor (D2R)	Depression and schizophrenia	Bristol-Myers Squibb	Nov-02	$2.8bn (2012)

The technologies for identifying individual GPCR drugs are now available and have opened up the field. The trouble with GPCRs until recently was that it was almost impossible to determine their structure. GPCRs are membrane-bound proteins that have seven membrane-spanning domains connected by intracellular and extracellular domains. Getting such complicated proteins out of the membrane in order to crystallise them was devilishly hard, because the required detergents would de-stabilise the receptor of interest and disrupt its

THE FIRST GPCR PLATFORMS WERE CREATED LESS THAN A DECADE AGO

[5] See omeros.com/pipeline/gpcr.htm.
[6] Nature Reviews Drug Discovery 5, 993-996.
[7] www.heptares.com/gpcrs.
[8] Or indeed what the mechanism of action was. Consider this line from the prescribing information for Seroquel: 'The mechanism of action of quetiapine is unknown'. That didn't stop Seroquel being a >US$5bn drug at its peak.
[9] There are around 800 GPCRs in the human genome but over half of them code for olfactory receptors.

conformational state[10]. This explains why the first structural solution of a human GPCR was only obtained in the year 2000[11]. Around 2007 or 2008, however, the technical problems around obtaining GPCR structures were more-or-less solved, which is one reason why Lefkowitz and Kobilka won their 2012 Nobels – the previous year Kobilka's group at Stanford had used one of the new techniques to obtain a crystal structure of the β2 adrenergic receptor at the exact moment that transmembrane signalling was taking place[12]. There were two basic solutions to problem of detergent-solubilised receptor-ligand complex stability, and each solution led to the creation of a GPCR platform company – Heptares for the 'thermostabilisation' technique[13] in 2007 and Receptos for the 'fusion partner' technique[14] in 2009. We argue that these companies have had the same effect on GPCRs as companies like Cambridge Antibody and Abgenix had on monoclonal antibodies in the 1990s and 2000s – opening up the field to new start-ups and making it easy for Big Pharma to fund development.

The early platforms went for high prices. It didn't take long for the first two GPCR platform companies to attract established pharma company interest, to the point where they were both acquired in 2015:

- Heptares[15] was bought in February 2015 by the medium-sized Japanese pharma company Sosei[16] for US$180m upfront and US$220m in milestone payments. Only one Heptares compound was in the clinic at the time of the acquisition (and that was in Phase I) but there were partnerships in place with AstraZeneca, Merck & Co.[17], MorphoSys and Takeda that had provided more than US$30m in upfronts and milestones.
- Receptos[18] was acquired by Celgene[19] in July 2015 for a massive US$7.2bn. The attraction for Celgene in part was that Receptos had advanced its lead candidate, Ozanimod, into Phase III in Inflammatory Bowel Disease and Multiple Sclerosis.

The Heptares and Receptos transactions doesn't end this game. We argue that there will be plenty of commercial interest to come in GPCRs and GPCR platforms.

[10] Because GPCRs switch regularly from the 'on' to the 'off' state depending on whether or not they are being bound by ligand, they tend to be less stable than other transmembrane proteins.
[11] Science. 2000 Aug 4;289(5480):739-45.
[12] Nature. 2011 Jul 19;477(7366):549-55.
[13] In which the GPCR is thermostabilised using systematic mutagenesis coupled with thermostability assays (see Nature. 2008 Jul 24;454(7203):486-91. Epub 2008 Jun 25.)
[14] In which a 'fusion partner' is inserted into one of the GPCR's intracellular loops (see Science. 2007 Nov 23;318(5854):1266-73. Epub 2007 Oct 25.). Receptos' methods are similar to those used by Kobilka.
[15] Welwyn Garden City, Hertfordshire, UK, www.heptares.com. This company originated from work done by Chris Tate and others at the UK's Medical Research Council Laboratory of Molecular Biology in Cambridge.
[16] Tokyo, Japan, TSE: 4565, www.sosei.com. As at 11 August 2016 Sosei was capitalised on the Tokyo Stock Exchange at US$2.6bn, versus an average US$21.2bn for the eight Japanese pharma companies in the Top 50 pharma companies globally.
[17] Via the antibiotics developer Cubist Pharmaceuticals, which Merck had bought in late 2014 for US$8.4bn.
[18] San Diego, Ca., www.receptos.com. Receptos was based on the work of Ray Stevens at the Scripps Research Institute.
[19] Summit, NJ, Nasdaq: CELG, www.celgene.com. Celgene was the world's 23rd largest pharma company in 2015 (source: Pharmaceutical Executive magazine).

- Ozanimod is one of only a few new GPCR-targeting drug to have come close to the market from the GPCR platforms, and that drug targets an already validated GPCR[20]. There remains plenty of other undrugged GPCRs – around 300-350 of them;
- There remains plenty of 'Orphan GPCRs' with no known ligand, even though Omeros has identified a few of these;
- Many well-known GPCRs have yet to be drugged even though the targets are well-validated and high value;
- There is huge potential upside from antibody therapeutics to GPCRs;
- The recent resurgence in drug discovery in the CNS field is likely to attract interest to GPCRs given the historical successes of drugs like Seroquel;
- Pain management could be revolutionised by GPCR heteromers - the side effects of opioid analgesics, whose mechanism of action involves GPCRs, can potentially be avoided through better targeting of GPCR heteromers[21];
- Other GPCR platform companies, most notably Trevena, Cara Therapeutics, and Arena Pharmaceuticals, continue to make progress with their programmes. Trevena in particular attracts a lot of attention if only because of its association with co-founder Robert Lefkowitz as well as the Breakthrough Desgnation for its lead programme, a pain drug now in Phase III.

THERE ARE A LOT OF ORPHAN GPCRS WITH NO KNOWN LIGAND

Medicine is likely to start looking at GPCR heteromers, using platforms like Dimerix's. Over the last five years a large body of work has built up around the science of GPCR heteromers, that is, individual GPCRs that complex together. Dimerix's core technology platform allows such GPCR heteromers to be identified and characterised. As more knowledge turns up concerning the utility of GPCR heteromers as drug targets, it's reasonable to expect Big Pharma to start turning its attention to these new targets, particularly since many are likely to be druggable with existing compounds. We believe that Dimerix can help prompt this reassessment of GPCR-targeting drugs with its own work on DMX-200 and other pipeline products.

WE THINK BIG PHARMA WILL SOON START TO BE INTERESTED IN GPCR HETEROMERS

Why Dimerix's platform is potentially very valuable

Why GPCR heteromers are the future of GPCR research. For a long time, it was thought that each single GPCR activated a linear signalling pathway to produce a single functional response. Then the GPCR homomers and GPCR heteromers – respectively combinations of the same GPCR or different GPCRs – started to be discovered. The emergence of the GPCR heteromers is a relatively recent phenomenon, with the first one, the $GABA_B$ heteromer[22] only being identified in 1998[23]. Many more have since turned up[24] due to the development of some

[20] The sphingosine 1-phosphate receptor pathway was already targeted by Novartis' Gilenya (fingolimod), which gained FDA approval in September 2010. Gilenya has a much longer half-life and pharmacodynamic effect than ozanimod, which gives the latter drug a better safety profile.
[21] See, for example, J Med Chem. 2014 Aug 14;57(15):6383-92. Epub 2014 Jul 18.
[22] Which allows the inhibitory neurotransmitter gamma-aminobutyric acid to exert its effect.
[23] Nature. 1998 Dec 17;396(6712):679-82.
[24] Most notably the beta 1 / beta 2-adrenergic receptor heterodimer in 2002 (see J Biol Chem. 2002 Sep 20;277(38):35402-10. Epub 2002 Jul 24); the delta/kappa opioid peptide receptor heteromer in 2005 (Proc Natl Acad Sci U S A. 2005 Jun 21;102(25):9050-5. Epub 2005 Jun 2); the AT1 / B2 receptor heterodimer in 2005 (J Mol Neurosci. 2005;26(2-3):185-92); the cannabinoid CB1 / dopamine D2L receptor heterodimer in 2009 (J Pharmacol Exp Ther.

powerful discovery tools, including those used by Dimerix. Indeed, since 1998 GPCR heteromers have been reported in such a wide variety of cells as to suggest that they are a general phenomenon of GPCRs. We argue that over the next two decades GPCR heteromers will become increasingly important as drug targets, and individual GPCRs of less and less importance, for three main reasons:

- **The ability of GPCR heteromers to involve new drug functions**. The main thing science has learned about GPCRs since 1998 is that when these receptors work together, they have a different 'biochemical fingerprint'. That is, they tend to behave in a considerably different fashion to the individual receptors in isolation. For example, when the dopamine D1 and D2 receptors in a heteromer are both stimulated by agonists, they produce intracellular calcium via a signaling pathway not activated by either receptor alone[25].
- **The ability to harness known drug functions more powerfully**. Often unrelated GPCRs come together in ways that are synergistic. As a good example of this, consider the SST_5-D_2 heteromer, the first heterodimerisation to be noted between relatively unrelated GPCRs[26]. SST_5-D_2 is the target of two neurotransmitters, somatostatin for SST_5 and dopamine for D_2. If you bind the D_2 receptor in this heteromer you boost the binding affinity of somatostatin to SST_5 and the downstream signalling is different as well.
- **The sheer abundance of new targets**. Given the large number of GPCRs, and their ability to form combinations, there may be tens or even hundreds of thousands of unique GPCR heteromers, greatly enlarging the pool of potential drug targets to be discovered with increased efficiency and selectivity compared with individual GPCRs.

THERE COULD BE HUNDREDS OF THOUSANDS OF GPCR HETEROMERS TO DISCOVER

Identifying GPCR heteromers is becoming easier. The main reason more and more GPCR heteromers have been discovered in recent years has been the use of two 'resonance energy transfer' techniques – fluorescence (FRET) and bioluminescence (BRET). What these techniques have in common is the measurement of energy moving between two light-sensitive molecules called 'chromophores'. When a donor chromophore is connected to one protein of interest in a cell, and then sends energy to an acceptor chromophore linked to another protein of interest, the resulting energy transfer, as measured by laboratory equipment, indicates that the two proteins are in close proximity and therefore potentially related in some way. FRET generally uses mutants of green fluorescent protein (GFP), which exhibit fluorescence when exposed to an excitation light[27], for its chromophores. BRET is a more advanced form of FRET where the acceptor chromophore is still a GFP mutant but where the donor chromophore is an enzyme called 'luciferase', which emits light naturally. Luciferase eliminates the need for an external light source which can sometimes interfere with detecting the natural energy transfer between chromophores[28]. Various groups around the world over the last six or seven years have been able to apply FRET and BRET to GPCRs. One of the leading groups created Dimerix's platform.

2010 Mar;332(3):710-9. Epub 2009 Dec 16); the bradykinin type 2 / beta 2 adrenergic receptor heteromer receptor in 2010(J Biomol Screen. 2010 Mar;15(3):251-60. Epub 2010 Feb 11); and the mGlu2 / mGlu4 receptor heterodimer in 2011 (FASEB J. 2011 Jan;25(1):66-77. Epub 2010 Sep 8).
[25] See J Biol Chem. 2004 Aug 20;279(34):35671-8. Epub 2004 May 24.
[26] Science. 2000 Apr 7;288(5463):154-7.
[27] A research tool so powerful that it won the 2008 Nobel Prize in Chemistry for the Americans Martin Chalfie and Roger Tsien and the Japanese Osamu Shimomura.
[28] Proc Natl Acad Sci U S A. 1999 Jan 5;96(1):151-6.

Dimerix owns the world's leading commercial GPCR heteromer discovery platform. The platform, called Receptor-Heteromer Investigation Technology ('Receptor-HIT'), is a patent-protected suite of BRET-based GPCR heteromer discovery tools. In its current form Receptor-HIT was invented around 2007 by Professor Karin Eidne and Associate Professor Kevin Pfleger at the Western Australian Institute for Medical Research (WAIMR), working in WAIMR's Laboratory for Molecular Endocrinology[29]. Kevin Pfleger, a Dimerix founder, remains involved as the company's Chief Scientific Advisor. Receptor-HIT works by co-expressing three proteins inside cells:

- The first GPCR of interest, attached to a luciferase such as Rluc8[30];
- The second GPCR of interest, left untagged; and
- A β-arrestin protein (which terminates G protein activation and sends the signal into the cell), tagged with a chromophore such as 'Venus', a yellow fluorescent protein (YFP)[31].

The ligand for the second GPCR is then thrown into the mix. The result is that the β-arrestin binds to the second GPCR (or the first if a transactivation event occurs). If there is then measurable energy transfer between the luciferase attached to the first GPCR and the YFP attached to the β-arrestin, it's a reasonable bet that the two GPCRs are a heteromer because they are in close proximity.

Dimerix believes that this platform is superior to other GPCR heteromer discovery techniques. For one thing, it's cell-based, so it can monitor GPCRs in real time in what is the GPCR's 'natural environment'. Secondly, it doesn't alter constituent receptor function, so that the heteromer can be quickly identified in its native tissue. Thirdly, it is ligand-dependent, meaning that only when the GPCR 'button' is being pressed by the right 'finger' will any signal show up the system. Obviously in an area of drug discovery evolving as fast as GPCRs are there are going to be competing platforms to identify GPCRs[32], just as there were for identifying the structure of single GPCRs. We argue that a significant competitive advantage of Dimerix's platform is that it has now generated products that are in the clinic.

DIMERIX'S PLATFORM IS CELL-BASED AND REAL-TIME

The Dimerix platform has started to yield drug candidates. Pfleger et. al. proved the utility of their platform through the discovery of the heteromer formed by angiotensin II receptor type 1 and chemokine (C-C motif) receptor 2, as well as the discovery *in vivo* that irbesartan and propagermanium, by targeting this heteromer, can successfully treat kidney disease[33]. We look at this programme, called DMX-200, in the next section of this report. Dimerix has also indicated that a pipeline is being built from other heteromers identified by the platform:

- **Nonalcoholic steatohepatitis (NASH).** Dimerix is now doing pre-clinical work on DMX-250, which is an angiotensin receptor blocker (but probably not irbesartan) plus propagermanium, this time targeted to NASH, a disorder in which fat builds up in the liver. NASH is understood to affect around 2-3% of the general population of most Western countries[34]. Dimerix announced in July 2016 that DMX-250 had performed well an animal model of NASH[35].

NASH WILL BE DIMERIX'S SECOND INDICATION

[29] See *Detection system and use therefor*, WO/2008/055313, priority date 10 November 2006.
[30] So called because it comes from an anthozoan called the sea pansy, *Renilla reniformes*, but has eight mutations in the protein.
[31] Nat Biotechnol. 2002 Jan;20(1):87-90.
[32] Such as the aforementioned FRET, as well as 'bimolecular fluorescence complementation', 'bimolecular luminescence complementation' and enzyme fragment complementation' – for a review see Drug Discov Today Technol. 2010 Spring;7(1):e1-e94.
[33] PLoS One. 2015 Mar 25;10(3):e0119803. eCollection 2015.
[34] Dig Dis. 2010;28(1):155-61. Epub 2010 May 7.
[35] See Dimerix's market release dated 28 July 2016 and headlined '*ASX Announcement- Dimerix Announces Pre-clinical Program, DMX-250, Targeting Heterodimers active in NASH, a major Liver Disease*'.

- **Diabetic retinopathy**. Dimerix's DMX-400 candidate is currently being readied for animal studies. Around 29% of US diabetics have vision-threatening retinopathy[36] for which treatment options are limited.
- **Cancer-related fatigue**. Dimerix has reportedly obtained some interesting *in vitro* data on a drug target considered relevant for the treatment of fatigue in cancer patients. We believe that the target in question for DMX-500 is probably a GPCR heteromer related to inflammation, given the growing body of knowledge around cancer fatigue mechanisms[37]. Estimates of the prevalence of cancer fatigue vary widely, but one carefully constructed prospective study has suggested that between 30% and 40% of cancer patients will be suffering from fatigue before, during and after their treatment[38]. No drug has ever come to the market specifically indicated for cancer fatigue.
- **Multiple Sclerosis (MS).** Dimerix's DMX-600 candidate, also the subject of *in vitro* work, is interesting because MS, while a near-Orphan indication[39], has grown into a multi-billion drug market in recent years thanks to the success of new products like Novartis' Gilenya and Biogen Idec's Tecfidera.

The platform is ideal for drug repurposing. We believe that DMX-200 has set a valuable precedent in that it shows how an off-patent GPCR-targeting drug can be repurposed. Moreover, it is reasonable to expect Dimerix to repeat its early achievement given the sheer number of existing GPCR-targeting drugs for which heteromer-specific activity can potentially be identified.

Big Pharma is interested in this platform. Dimerix notes quietly in its presentations that there are currently MSAs in place with two 'Top Pharma' companies. We think this collaborative interest by large pharma companies has the potential to evolve into a Heptares/Sosei-style transaction should DMX-200 yield valuable data in the current Phase II studies.

DMX-200 – A valuable lead Orphan Drug

DMX-200 is two approved drugs put together. DMX-200 is the well-known hypertension drug irbesartan, adjuncted with a less-well-known anti-inflammatory drug called propagermanium, for the treatment of kidney disease. The first approved indication for DMX-200 is expected to be an Orphan kidney disorder called Focal Segmental Glomerulosclerosis (FSGS). The product originated from work done in the Pfleger lab showing that AT1R and CCR2, both GPCRs, form a GPCR heteromer that is highly relevant in kidney disease. Irbesartan works by binding AT1R, while propagermanium works by binding to CCR2. *In vivo*, DMX-200 has shown a significant reduction in proteinuria, that is, protein leaking into the urine, in an animal model of kidney disease, which is highly indicative of efficacy overall. The product is in Phase II in patients with proteinuria, which is symptomatic of a range of kidney problems, and in June 2016 Dimerix obtained FDA guidance related to a pathway for DMX-200

DMX-200 IS TWO APPROVED DRUGS PUT TOGETHER

[36] JAMA. 2010 Aug 11;304(6):649-56.
[37] Brain Behav Immun. 2013 Mar;30 Suppl:S48-57. Epub 2012 Jul 6.
[38] Br J Cancer. 2011 Jul 26; 105(3): 445–451.
[39] Neurology. 2002 Jan 8;58(1):136-8.

into Phase III in FSGS. To understand the potential of DMX-200 in kidney disease, let's look at its two constituent drugs and then kidney disease itself before looking at the combination.

- **Irbesartan** is the generic name for Avapro, a former blockbuster drug from Sanofi and Bristol-Myers Squibb for the treatment of hypertension which gained its original FDA approval in 1997. Avapro wasn't the first of the angiotensin II receptor blockers – that was Merck & Co.'s Cozaar (losartan), FDA approved in 1995 – but it was more efficient in terms of lowering blood pressure and had a longer half-life[40]. The drug's peak sales were US$2.7bn before the end of patent life in early 2012. Angiotensin II receptor blockers represented a big step forward in the treatment of high blood pressure because they offered better control over the renin-angiotensin system than their predecessor class, the ACE inhibitors[41]. Since high blood pressure tends to damage the kidneys over time they also represented a step forward in the renal area. Avapro gained FDA approval for the treatment of diabetic nephropathy (that is, kidney damage caused by high blood sugar levels) in 2002.
- **Propagermanium** is a much-less well known drug than irbesartan, since its only approved use to date has been in Japan, for the treatment of Hepatitis B infection. The drug was originally developed by a small Japanese pharmaceutical company called Sanwa Kagaku and gained the Japanese Hepatitis B approval in 1994. Propagermanium, an organic germanium compound[42], doesn't act directly on Hepatitis B virus and its mechanism of action in Hepatitis B is poorly understood but believed to involve restoration of virus-specific cellular immunity[43]. However, much research interest since the mid-1990s has focused on propagermanium's anti-inflammatory properties, which is effected by blocking the chemokine receptor CCR2[44]. Short for C-C motif chemokine receptor type 2, CCR2 binds to the cytokine MCP-1 (monocyte chemo-attractant protein 1), which in turn promotes migration of monocytes. CCR2 antagonists, by preventing this migration, can blunt a potentially damaging immune response.
- **Why these two drugs?** When Pfleger and his colleagues considered which small molecule would be ideal to drug the constituent GPCRs of their heteromer, it wasn't hard to select irbesartan, as the best of the angiotensin receptor blockers, to drug AT1R, given that by 2012 it was going off-patent. For CCR2 the choice was more complicated since there was no approved drug targeting this GPCR. Propagermanium, however, had gained at least one regulatory approval, and over the years had built a following in the US as a dietary supplement due to its potential anti-cancer properties[45]. This made it relatively easy to source[46]. Apart from the need to provide the drug to Australian patients under Special Access[47], the only downside to using propagermanium was that at the doses suggested from the animal data it would have

[40] See Can J Clin Pharmacol. 2000 Spring;7(1):22-31.
[41] Renin is a hormone produced by the kidneys whenever the body senses that blood pressure has become too low. Renin then converts angiotensinogen into Angiotensin I, which is then converted by angiotensin-converting enzyme (ACE) into Angiotensin II. This final hormone is a powerful vasoconstrictor, that is, it constricts blood vessels, which increases blood pressure.
[42] That is, the chemical element with symbol Ge and atomic number 32. Propagermanium is a hydrophilic polymer of 3-oxygermyl propionate.
[43] J Gastroenterol. 2003;38(6):525-32. The speed of this immune response can cause liver damage in some patients. When this issue was first identified, around 1995, Japan's Committee on Adverse Drug Reactions ordered a special warning on the drug's packaging but did not withdraw marketing authorisation.
[44] J Interferon Cytokine Res. 2001 Jun;21(6):389-98.
[45] See, for example J Biol Response Mod 1985;4:159-168.
[46] For some background here from a true believer in propagermanium (also called GE-132 or Germanium sesquioxide), see www.germaniumsesquioxide.com. The FDA has a current 'import alert' on this product due to non-US manufacturing issues that date back to the 1980s (See FDA Import Alert 54-07).
[47] Since it is not approved in Australia. For a recent announcement on Special Access see Dimerix's market release dated 19 April 2016 and headlined '*Dimerix Receives TGA Special Access Scheme Approval to Continue to Supply Propagermanium to Kidney Patients on its DMX-200 Phase II trial*'.

to be taken three-times daily. Dimerix is now working with consulting chemists on a novel extended-release propagermanium that will also provide some extra intellectual property over the irbesartan/propagermanium combination.

If Dimerix is right, >10% of the population of the US and Europe could be helped with DMX-200. Currently around 12% of the US population has CKD and the European experience is probably similar[48]. The reason for this large patient population has to do with the ease with which kidneys can be damaged by Western lifestyles. The major function of the kidneys is to remove waste products and excess fluid from the blood. Within each kidney are up to a million 'filtration units' called nephrons. Each nephron has a capillary feeding into it called a glomerulus which performs the filtration function, after which the excess fluid flows into a tubule that carries the waste out of the body, ultimately in the form of urine. High blood pressure and diabetes will tend to damage the kidneys by exerting pressure on the glomeruli and other parts of the kidney. An early warning sign of kidney disease is proteinuria, that is, the blood protein albumin leaking into the urine, which can happen when the glomeruli become scarred and therefore less effective. This is the main symptom of nephrotic syndrome, which could be described as something of a warm-up act for the headliner of Chronic Kidney Disease (CKD), where the actual filtration function of the kidney, as measured by the estimated Glomerular Filtration Rate (GFR)[49], has noticeably fallen, and continues to do so through four stages of CKD until Stage 5. At that stage, better known as End-Stage Renal Disease (ESRD), there is virtually no kidney function left and the patient has to rely on dialysis if he or she can't find a donor kidney. The decline in kidney function in CKD, which the patients starts to feel by about Stage 3, manifests itself in swelling[50], tiredness and poor appetite among other things, as toxic wastes which should have been filtered by kidney build up in the blood. Eventually the toxic wastes can lead to the death of the patient at the time of ESRD through organ failure of some kind. The reason why there is so much CKD around is that it tends to travel in lockstep with hypertension and Type 2 Diabetes, where prevalence figures are also regrettably high - respectively 29%[51] and 12%[52] in US adults.

12% OF THE US POPULATION HAS CHRONIC KIDNEY DISEASE

Why DMX-200 could be the Next Big Thing in kidney disease. Prior to developing DMX-200, Pfleger et. al. had some valuable help from the literature. Scientists had long suspected that the renin-angiotensin system and the immune system were linked, and by 2011 it had been established that the blockade of AT1R and CCR2 could be effective in the treatment of kidney disease[53]. The Pfleger group's main insight, gained during 2011[54] through the use of Receptor-HIT, was that the two receptors formed a GPCR heteromer. Having determined this, they then blockaded the heteromer with irbesartan and propagermanium in the 'gold-standard' animal model of CKD, the

[48] J Am Soc Nephrol. 2006 Aug;17(8):2275-84. Epub 2006 Jun 21.
[49] Measured by testing for the blood levels of creatinine, a breakdown product of muscle. Creatinine is normally cleared from the blood by the kidneys. When kidney function is declining the level of creatinine in the blood goes up.
[50] The loss of albumin leads to edema, that is, fluid retention.
[51] NCHS Data Brief. 2013 Oct;(133):1-8.
[52] JAMA. 2015 Sep 8;314(10):1021-9.
[53] In 2007 a group at Tulane University in New Orleans had shown that angiotensin II infusion in rats activated MCP-1 (the ligand to CCR2) which induced macrophage infiltration of renal tissues (Am J Physiol Renal Physiol. 2007 Jan;292(1):F330-9. Epub 2006 Jun 27). A follow-up study by the same group in 2011 showed that combined treatment with a CCR2 antagonist and an angiotensin receptor blocker could treat a renal condition called crescentic glomerulonephritis in an animal model (Hypertension. 2011 Mar;57(3):586-93. Epub 2011 Jan 31).
[54] See *Combination therapy*, WO/2012/094703, priority date 11 January 2011.

STNx model. The results, as published in the journal PLOS ONE in March 2015[55], were highly favourable, with each change compared to untreated controls having statistical significance:

- a >60% drop in the level of proteinuria in the treated rats. This was something neither irbesartan and propagermanium on their own could achieve, and important given that reductions in proteinuria of greater than 50% have long been considered clinically meaningful[56];
- A >70% drop in macrophage infiltration into the renal area;
- An 40% improvement compared to untreated controls in podocytes, that is, the cells which surround the glomeruli.
- An improvement in fibrosis, in both the glomeruli and the tubules.

IN VIVO DMX-200 CUT PROTEINURIA BY MORE THAN HALF

The main reason why this data is promising is that until now kidney disease has been widely treated with blood pressure drugs including irbesartan, but there has been relatively little advance in terms of blunting damage to the kidneys caused by inflammation beyond the use of steroids. In the PLOS ONE paper Pfleger et. al. showed that when AT1R and CCR2 were co-expressed in a cell, the CCR2 signal in terms of G proteins induced by its natural ligand, CCL2, was much stronger when AT1R was being bound by its natural ligand, AngII, at the same time. In other words, the existence of the AT1R/CCR2 heteromer means a stronger level of inflammation notionally being directed towards kidney cells than was previously understood. By blocking this inflammation, there is potentially much less damage to the glomeruli as well as other tissue.

CCR2 IS A VALIDATED TARGET IN KIDNEY DISEASE

ChemoCentryx have validated CCR2 as a target in kidney disease. ChemoCentryx[57] is a US drug developer focused on chemokines. Their lead molecule is CCX140, a CCR2 inhibitor that has completed Phase II in diabetic nephropathy. In December 2014 ChemoCentryx reported a statistically significant reduction in proteinuria for patients treated on the lower of two doses of CCX140 of 18% over 52 weeks (p=0.01) that were also on the standard-of-care of either ACE inhibitors or angiotensin receptor blockers. ChemoCentryx's investigators also noted an improvement in eGFR alongside the reduction in proteinuria[58]. The Phase II data were published in August 2015[59]. We believe this work validates the approach that Dimerix is taking with the use of a CCR2 antagonist to reduce proteinuria[60].

DMX-200 is in Phase II in patients with proteinuria. In late 2014 Dimerix initiated a Phase II study of DMX-200 at various sites in Melbourne in patients with proteinuria[61]. The choice of simply the proteinuria symptom rather than outright nephrotic syndrome or CKD was deliberate, with Dimerix taking the view that it simply needs to establish that DMX-200 can take down proteinuria, in line with the *in vivo* data, and that favourable effects in terms of both nephrotic syndrome and CKD can potentially follow. DMX-200's Phase II is running in two parts:

[55] PLoS One. 2015 Mar 25;10(3):e0119803. eCollection 2015.
[56] See, for example, Kidney Int. 2004 Jun;65(6):2309-20.
[57] Mountain View, Ca., Nasdaq: CCXI, www.chemocentryx.com.
[58] See the company's market release dated 12 December 2014 and headlined '*ChemoCentryx Announces Positive Results in Phase II Diabetic Nephropathy Trial With CCR2 Inhibitor CCX140*'.
[59] Lancet Diabetes Endocrinol. 2015 Sep;3(9):687-96. doi: 10.1016/S2213-8587(15)00261-2. Epub 2015 Aug 9.
[60] There are potentially also lessons on patient selection from this study which Dimerix will likely consider, such as the use of biomarkers that indicate the best responses to a CCR2 antagonist.
[61] ANZCTR trial ID ACTRN12614001132639.

- **Part A – Dose Ranging Study**. An initial dose-ranging study in 30 patients will treat each irbesartan-managed patient at ascending doses of propagermanium[62] to demonstrate safety and reduction or remission of proteinuria, and maintain the dose that achieves this for a further eight weeks. Dimerix dosed the 10th patient in this study in June 2016 and expects to read out interim data from this cohort in the third quarter of 2016. The study itself is expected to complete in mid-2017.
- **Preparation for Part B**. Dimerix will need to conduct pharmacokinetic work in animals to show that its extended-release formulation of propagermanium is equivalent to the current formulations, after which it intends to file the IND, then complete formal human PK studies of the extended release formulation.
- **Part B – Expansion Study.** With this study the average successful dose from Part A will be administered to another 30 patients over 84 days beginning in the second half of 2017. The primary endpoint of the Phase II is safety, but Dimerix will also be looking for Complete or Partial Remissions of proteinuria as either a co-primary or a secondary endpoint.

After Phase II, DMX-200 will go to Phase III in Focal Segmental Glomerulosclerosis, one of several notable nephrotic syndromes[63]. Dimerix chose FSGS, where only some of the glomeruli are scarred ('focal') and where glomeruli are affected the scarring is only in part ('segmental'), as the initial target indication for DMX-200 for five reasons:

- It is an Orphan indication with benefits to Dimerix in terms of the path to market[64]. DMX-200 was granted Orphan Drug status in FSGS in December 2015;
- Beyond high-dose prednisone, which only brings about a complete response in one third of patients[65], and another expensive agent called Acthar Gel, neither of which are suitable for long-term use, there are no available treatment options for FSGS;
- The level of unmet medical need is high given that FSGS is often idiopathic and around 30% of patients will have failing kidneys within five years[66];
- For those patients fortunate enough to obtain a kidney transplant[67], around 30% will end up with recurrent FSGS[68];
- The disease is primarily driven by proteinuria, so dealing with this condition can likely make a difference in FSGS patients[69].

Dimerix's pre-IND meeting with the FDA was encouraging. The meeting, in late June 2016, sought regulatory guidance from the Agency on the proposed FSGS indication. Coming away from this meeting, Dimerix believes that, after the current Phase II work, it can potentially take DMX-200 into a single pivotal study of less than 100 patients where reduction in proteinuria could be an approvable endpoint and early data review an option.

DMX-200'S PIVOTAL STUDY COULD BE <100 PATIENTS

[62] 30mg, 60mg, 90mg, 150mg, 240mg per day with the dose ascending every four weeks.
[63] The others include 'Minimal Change Disease', 'Membranous Nephropathy' and 'Membranous Glomerulonephritis'.
[64] The significant incentives for developers of Orphan Drugs, as outlined in America's The Orphan Drug Act of 1983, include: a) US Federal tax credits for up to 50% of the research costs; b) seven years of US market exclusivity for the approved indication; c) waivers of PDUFA fees; d) research grants to defray clinical development costs; and e) protocol assistance from the FDA.
[65] Am J Kidney Dis. 1995 Apr;25(4):534-42.
[66] Clin Nephrol. 1991 Aug;36(2):53-9.
[67] Only around 1,000 FSGS patients in America receive a kidney transplant annually – source: Variant Pharma.
[68] Clin Transplant. 2011 Jul;25 Suppl 23:6-14.
[69] It is estimated that proteinuria in FSGS patients can be 25 times higher than in diabetic nephropathy patients – see Am J Physiol Renal Physiol. 2008 Dec;295(6):F1589-600. Epub 2008 Jun 25. One Canadian study has found that a reduction in proteinuria is the main factor in renal survival for FSGS patients – see J Am Soc Nephrol. 2005 Apr;16(4):1061-8. Epub 2005 Feb 16.

Encouragingly, the Agency appears to agree with Dimerix that DMX-200 is an adjunct therapy, where the propagermanium is adjunctive to ibersartan. This means that the questions of safety aren't around the combination, but around propagermanium for patients already on irbesartan, which reduces the number of patients needed at Phase III.

What's the patient population for DMX-200 in FSGS? The epidemiology around FSGS is sketchy but we estimate there are somewhere between 25,000 and 50,000 FSGS patients in the US.

- For the lower figure assume 3.0 new nephrotic syndrome cases per 100,000 US adults[70] and 2.5 cases per 100,000 children[71]; 40% of adult cases and 20% of child cases being FSGS[72]; and an average life expectancy from diagnosis of 8 years[73];
- For the upper figure consider that in 2010 around 24,000 people[74], or 4.1% of all the people with ESRD in the United States, had a primary diagnosis of FSGS[75]. Allowing five to ten years for those patients to accumulate suggests an FSGS patient population of ~50,000.

Can FSGS be a large market opportunity in the US? In recent years, healthcare systems have started to encounter the phenomenon of increasing numbers of Orphan drugs selling at what seems like very high prices[76], in some cases allowing the drugs to become blockbusters. The high price tags are partly a result of the cost effectiveness of drugs that remove substantial treatment costs.

- New drugs that treat Orphan kidney diseases and thereby avoid ESRD in the treated patients have high pricing potential because a kidney transplant in the US can cost >US$330,000[77] while dialysis can cost US$70,000-85,000 per year[78].
- The benchmark agent in recent years has been the aforementioned H.P. Acthar Gel, a repository corticotropin injection that was FDA approved in the 1950s[79] and which has recently been found to be effective in FSGS patients that are steroid-resistant. Acthar now reimburses in the US at US$35,000 for a 5 ml vial[80], which at the suggested dosage rates[81] would cost >US$360,000 for a six-month course of treatment. Acthar Gel has been marketed for use in nephrotic syndrome since 2011. Dimerix believes that around half of Acthar's 2012 sales of US$509m were for this indication[82] and that continued use in nephrotic syndrome contributed to US$761m in 2013 sales. It was this kind of success which encouraged

FSGS DRUGS CAN COME WITH A HIGH PRICE-TAG

[70] BMJ : British Medical Journal. 2008;336(7654):1185-1189.
[71] Clin Nephrol. 2012 Aug;78(2):112-5.
[72] Clin Nephrol. 2005 Jan;63(1):1-7 and Pediatr Nephrol. 1999 Jan;13(1):13-8.
[73] Estimated using treatment success data from Saudi J Kidney Dis Transpl. 1994 July-September;5(3):354-8. It has been suggested by one group that 70% of FSGS patients can respond to corticosteroids or immunosuppressive drugs and maintain stable renal function for about 10 years – see Am J Kidney Dis. 1999 Oct;34(4):618-25
[74] See Table B7, US Renal Data System, 2012 Annual Data Report, Atlas of End Stage Renal Disease in the United States.
[75] The prevalence of FSGS in the US ESRD patient population has been rising, from 0.2% in 1980 to 2.3% in 2000 – see Am J Kidney Dis. 2004 Nov;44(5):815-25.
[76] See, for example, *The World's Most Expensive Drugs* by Matthew Herper, Forbes, 22 February 2010.
[77] Source: *US organ and tissue transplant costs estimates and discussion*, Milliman, December 2014.
[78] US$70,000 per year for peritoneal dialysis, US$85,000 for hemodialysis in 2013. Source: US Renal Data System 2015 Annual Data Report.
[79] See www.acthar.com. Acthar gel is a highly purified preparation of adrenocorticotropic hormone, the pituitary hormone which stimulates the adrenal gland to make cortisol, a corticosteroid.
[80] See *Mallinckrodt's $35,000 Drug Is Back in the Spotlight* by Cynthia Koons and Robert Langreth, Bloomberg, 10 November 2015.
[81] Clin J Am Soc Nephrol. 2013 Dec 6; 8(12): 2072–2081.
[82] See Dimerix's 16 September 2015 presentation, slide 16.

Mallinkrodt Pharmaceuticals[83] to buy Acthar's owner, Questcor Pharmaceuticals, for US$5.6bn in August 2014.

AT THE RIGHT PRICING DMX-200 COULD BE A BLOCKBUSTER

To become a blockbuster in the US an FSGS drug serving 40,000 patients only needs to sell for US$25,000 pa. Obviously it is early days in the life of DMX-200 as a programme, but given that that the generally-accepted threshold for cost effectiveness in the US is US$50,000 to US$100,000 per Quality-Adjusted Life Year[84], that kind of outcome seems feasible. The attractiveness of FSGS as a relatively neglected patient population helps explains why the private Australian biotech company Fibrotech Therapeutics was acquired by Shire[85] in May 2014 for US$75m upfront and US$482.5m in milestones. At the time Fibrotech was in a Phase 1b study in diabetic nephropathy with an anti-fibrosis small molecule FT011[86], on a pathway towards a Phase II in FSGS.

The enlarged market opportunity is significant. In the US around 15% of the population over the age of 20 has CKD, making for a patient population of 36 million people. The first two stages of the disease are fairly mild, however that still leaves 8.3% of the adult population, or 20 million people, with Stage 3 and 4 disease characterised by moderate to severely reduced kidney function[87]. A further ~700,000 people have ESRD[88]. We believe that DMX-200 has the potential to expand beyond its initial FSGS indication and go after this larger patient population. The high prevalence of CKD suggests a strong market opportunity which we believe is today is worth >US$10bn[89].

- The field has in the past created two notable blockbusters, Epogen[90] and Sensipar[91];
- As an indication of the upside in terms of a relatively early transaction, consider that the Swiss company Galenica[92] agreed in July 2016 to buy the US biotech company Relypsa[93], developer of a potassium binder[94] called Veltassa, for US$1.5bn. Veltassa had only gained FDA approval in October 2015;
- Keryx Biopharmaceuticals[95] is now a >US$450m company[96] thanks to the September 2014 FDA approval of Auryxia (ferric citrate), an iron-based phosphate binder for dialysis patients suffering hyperphosphatemia.

[83] Chesterfield, United Kingdom, NYSE: MNK, www.mallinckrodt.com. Mallinckrodt became the world's 40th largest pharma company in 2015 (source: Pharmaceutical Executive magazine).
[84] N Engl J Med 2014; 371:796-797.
[85] Dublin, Ireland, Nasdaq: SHPG, www.shire.com. Shire was the world's 30th largest pharma company in 2015 (source Pharmaceutical Executive magazine).
[86] The drug appears to work partly by attenuating TGF-ß induced collagen synthesis.
[87] Source: NHANES 2007-2014 data.
[88] For quarterly figures see the United States Renal Data System at usrds.org.
[89] Suggested by US Medicare data for 2013 where Part D spending for CKD patients was 46% higher than for general Medicare patients, at US$3,675 per patient (source: US Renal Data System).
[90] Epogen, the first of the erythropoietin stimulating agents. This product, Amgen's foundation drug, replaces the erythropoietin hormone ordinarily synthesised in the kidneys but which a failed kidney can no longer produce. At its peak in 2004 Epogen was a US$2.6bn drug for Amgen.
[91] Sensipar, a calcium mimetic. This Amgen drug treats secondary hyperparathyroidism, which is what happens when failed kidneys throw the body's management of calcium and phosphorus out of line. Sensipar was a US$1.4bn drug for Amgen in 2015.
[92] Bern, Switzerland, SIX: GALN, www.galenica.com.
[93] Redwood City, Ca., Nasdaq: RLYP, www.relypsa.com.
[94] Patients with CKD have difficulty managing the level of potassium, calcium and phosphorus in the blood. Binders help keep these elements under control.
[95] Boston, Ma., Nasdaq: KERX, www.keryx.com.
[96] US$459m market capitalisation at 22 August 2016 close on Nasdaq.

Valuing Dimerix

We valued Dimerix $0.024 per share base case and $0.059 per share optimistic case using a probability-weighted DCF approach. Our approach was as follows:

WE VALUE DIMERIX AT 2.4 CENTS BASE CASE AND 5.9 CENTS OPTIMISTIC CASE

- Our WACC was 14.5% (Speculative)[97].
- We conservatively modelled a payoff only for DMX-200 and allowed no value for the Dimerix pipeline. We believe *in vivo* data from the pipeline will allow us to gradually add value from this platform.
- We assume another US$5-10m in expenditure for Dimerix to mature the DMX-200 programme.
- We model around 14 years of commercial exclusivity for DMX-200.

Risk weighting

- We modelled DMX-200 with a 50% probability of clinical success. This may seem high given the product is still only at Phase II, however the *in vivo* evidence of efficacy in lowering proteinuria, and the importance of this endpoint to disease outcomes in FSGS, as well as the ease with which DMX-200 can enter Phase III in FSGS, suggested a more favourable risk weighting for this product.

Commercial outcomes

- We assume that the product can license to a pharma partner in FY19 (base case) or FY18 (optimistic case) for US$30-50m upfront, US$100-200m in milestones and an 8-12% royalty.
- We assume a product launch in FSGS in FY22 (base case) or FY21 (optimistic case) in the US and FY23 (base case) or FY22 (optimistic case) in Europe.
- We assume peak sales for DMX-200 of US$300-600m, initially in FSGS and then branching out into other kidney disorders.

Further capital

- An admirable feature of Dimerix since listing has been the low burn rate, averaging only ~A$130,000 per months for the last twelve months. However, with only A$2m cash as at June 2016, we believe it will be necessary for Dimerix to raise further capital. For modelling purposes, we assume that the company raises another $10m at $0.01 per share (which was the price of the mid-2015 raising) in order to complete both halves of the current Phase II for DMX-200 as well as move other pipeline elements forward.

[97] 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 1.9%; a MRP of 7.5%-11.5% (7.5% for 'medium risk' companies, 9.5% for 'high risk' companies and 11.5% for 'speculative' companies like Dimerix); 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'.

Re-rating Dimerix

We see a number of events helping to re-rate Dimerix to our target price over the next 12-18 months:

- Interim data from DMX-200's Phase IIa study;
- Completion of recruitment for the Phase IIa study;
- Completion of the extended-release formulation of propagermanium;
- Data from the Phase IIa study;
- Research agreements and collaborations related to the Receptor-HIT platform;
- Pre-clinical data from DMX-250 in NASH;
- Data from the other pre-clinical programmes from Receptor-HIT;
- Filing of the IND for DMX-200;
- Ethics approval and initial patient recruitment for the first Part B sites.

DATA FROM DMS-200's PHASE II STUDY WILL BE AVAILABLE SHORTLY

Dimerix's strong leadership team

Dimerix has a strong leadership team with the necessary skills to take drugs to market.

Dr James Williams (Executive Chairman) has a track record of success in the Life Sciences sector gained over many years and various kinds of companies:

- **Argus Biomedical**. This Perth-based company, which Williams ran from 2000 to 2002, brought to market the AlphaCor, the world's first soft one-piece artificial cornea, which gained FDA approval in August 2002. The product was acquired by the Cooper Companies in 2004.
- **Resonance Health**[98]**.** This company, which was commercialising a non-invasive MRI-based diagnostic to measure iron levels in the liver, gained its first regulatory approval and made its initial market launch during Williams' term as CEO between 2004 and 2006.
- **iCeutica,** of which Williams was a co-founder in 2005, was built around drug reformulation technology called SoluMatrix. With this dry milling process, submicron particles of commercially available drugs can be engineered, enabling those drugs to be delivered at lower doses. iCeutica was acquired by the US drug developer Iroko Pharmaceuticals[99] in April 2011, and that company has since secured multiple FDA approvals for drugs formulated using the SoluMatrix platform. The price that Iroko paid for iCeutica is reportedly 'more than 10 times the closing valuation of its first fundraising round'[100], which had happened less than six years' previously.
- **Yuuwa Capital.** This A$40 million venture capital fund founded by Williams in 2009 has had a number of successful investments including Adalta[101] (an antibody engineer), PolyActiva[102] (a developer of drug-

JAMES WILLIAMS WAS AN ICEUTICA CO-FOUNDER

[98] Perth, Australia, ASX: RHT, www.resonancehealth.com.
[99] Philadelphia, Pa., privately held, www.iroko.com.
[100] See *iCeutica Sale To Iroko Pharmaceuticals Finalised,* Asian Scientist Newsroom, 29/4/2011
[101] Brisbane, Australia, ASX: 1AD, www.adalta.com.au
[102] Melbourne, Australia, privately held, www.polyactiva.com.

polymer conjugates, allowing site-specific drug delivery from implantable devices) and Nexgen Plants[103] (a plant genetics company).

Kathy Harrison (General Manager) brings to Dimerix a background in IP law honed as a patent attorney, as well as more generalist skills gained at two Australian biotech companies – Cytopia and Phosphagenics. Under Kathy Dimerix has secured a solid IP position for the Receptor-HIT platform and for DMX-200, as well as moved DMX-200 into the clinic.

Associate Professor Kevin Pfleger (Chief Scientific Advisor) as an authority on the use of BRET for the study of GPCRs, has enabled Dimerix to lead the relatively new field of GPCR heteromer research with an elegant technology easily adaptable to high throughput screening. Pfleger's willingness to serve as Chief Scientific Advisor of Dimerix provides the company with valuable 'technology memory'.

KEVIN PFLEGER BRINGS VALUABLE 'TECHNOLOGY MEMORY'

Dr Sonia Poli (Non-Executive Director) brings drug design smarts to Dimerix from her time at Roche and at the Swiss GPCR-focused drug design company Addex Therapeutics[104], where she is currently Chief Scientific Officer.

David Franklyn (Non-Executive Director), whose background in stockbroking and funds management, was for a number of years Chairman of the Melbourne biotech company Calzada.

Dr Liz Jazwinska (Non-Executive Director), as a senior executive in the Australian arm of J&J, brings valuable pharma licensing and partnership knowledge to Dimerix.

[103] Brisbane, Qld, privately held, www.nexgenplants.com.
[104] Geneva, Switzerland, SIX: ADXN, www.addextherapeutics.com.

Risks related to Dimerix

Risks specific to Dimerix. We see five major risks for Dimerix as a company and as a listed stock.

- **Timing risk.** There is the risk that Dimerix may take longer to complete the first part of the clinical work for DMX-200 than the time we have postulated in this note;
- **Clinical risk.** There is the risk that the current Phase II or the forthcoming pivotal study for DMX-200 may miss its primary or secondary endpoints.
- **Regulatory risk.** There is the risk that the FDA and other regulators may decline to approve DMX-200 even if Dimerix consider the data submitted to be adequate.
- **Formulation risk**. There is the risk that propagermanium may not be adaptable in to an extended release formulation.
- **Commercial risk**. There is the risk that DMX-200 may be displaced by other more advance therapies in kidney disease, particularly those related to regenerative medicine.

Risks related to pre-revenue Life Science companies in general.

- The stocks of biotechnology and medical device companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character.
- Since most biotechnology and medical device companies listed on the Australian Securities Exchange fit this description, the 'term' speculative can reasonably be applied to the entire sector.
- The fact that the intellectual property base of most biotechnology and medical device lies in science not generally regarded as accessible to the layman adds further to the riskiness with which the sector ought to be regarded.

Caveat emptor. Investors are advised to be cognisant of the abovementioned specific and general risks before buying any the stock of any biotechnology and medical device stock mentioned on this report, including Dimerix.

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General Advice Warning.

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Recommendations

NDF Research issues a BUY recommendation in case of an expected total shareholder return (TSR, share price appreciation plus dividend yield) in excess of 25% within the next twelve months, an ACCUMULATE recommendation in case of an expected TSR between 5% and 25%, a HOLD recommendation in case of an expected TSR between -5% and +5% within the next twelve months and a SELL recommendation in case of an expected total return lower than -5% within the next twelve months.

Contact Details

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Appendix I – A Dimerix glossary

Adjunct therapy – Therapy that is given in addition to the initial therapy. In studies of DMX-200 propagermanium is considered adjuctive to irbesartan.

Angiotensin – A hormone involved in the maintenance of blood pressure and fluid balance. There are various types of angiotensin. The one that raises blood pressure, through the constriction of blood vessels, is angiotensin II.

Angiotensin II Type 1 receptor (AT1R) – An angiotensin receptor important in the control of blood pressure. AT1R is the target of Irbesartan.

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

Bowman's capsule – A cup-like sac which surrounds a glomerulus. Bowman's capsules are made up of podocytes.

BRET – Short for Bioluminescence Resonance Energy Transfer, BRET is the transfer of energy from a bioluminescent donor enzyme to an acceptor fluorophore. Dimerix uses BRET to identify GPCR heteromers.

C-C motif chemokine receptor type 2 (CCR2) – A chemokine receptor that binds to the cytokine MCP-1 (monocyte chemo-attractant protein 1), which in turn promotes migration of monocytes. CCR2 is targeted by propagermanium.

Chemokine – Cell signalling molecules that direct immune cells to migrate towards the site of a required immune response.

Chronic Kidney Disease (CKD) – Gradual loss of kidney function over time, as measured by eGFR.

Diabetic retinopathy –A disease of the small blood vessels of the retina in the eye that originates from the diabetic condition of the patient. Diabetic retinopathy results in blurred vision and ultimately blindness.

Dimer – A chemical structure formed from two sub-units.

DMX-200 – Dimerix's lead candidate, which is irbesartan plus propagermanium.

DMX-250 – Dimerix's candidate for the treatment of NASH, which is an angiotensin receptor blocker plus propagermanium.

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

eGFR – See Glomerular Filtration rate.

End-Stage Renal Disease (ESRD) – Stage 5 of Chronic Kidney Disease in which the patient has virtually no kidney function left. ESRD is treated either with dialysis or kidney transplant.

Fibrosis – Scarring and thickening of tissue, thereby weakening tissue function.

Focal Segmental Glomerulosclerosis (FSGS) – A rare nephrotic syndrome disorder in which only some of the glomeruli are scarred ('focal') and where glomeruli are affected the scarring is only in part ('segmental').

Glomerular Filtration Rate (GFR) – An estimate of kidney function as measured in millilitres/minute/1.73m^2, the latter figure being the average body surface area for an adult.

Glomerulus – A capillary (the plural is glomeruli) within the kidneys which filter the blood.

G Protein-Coupled Receptor (GPCR) – A protein on the surface if cells whose function is to transduce extracellular stimuli into intracellular signals.

Heteromer – In biology, a complex formed from several types of subunit. For example, the Mu/Delta Opioid Receptor Heteromer is a complex of the Mu Opioid Receptor and the Delta Opioid Receptor.

Hypertension – High blood pressure.

Idiopathic – A disease which arises spontaneously or for which the cause is unknown.

IND – Short for Investigational New Drug application, a request filed with the FDA for authorisation to conduct human trials of a new drug or biological product in the United States.

In vivo – Latin for 'in life', referring to data obtained through testing in live organisms including animal models and humans.

Irbesartan – An angiotensin II receptor blocker that, by relaxing blood vessels, can lower blood pressure. Irbesartan is one part of Dimerix's lead DMX-200 product.

Kidneys – Organs which filter blood and carry waste to the bladder.

Ligand – Pronounced 'lee-gand'. A molecule that binds to another molecule.

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.

Multiple Sclerosis – An autoimmune disorder in which the immune system attacks the myelin sheath of axons, leading to numbness, co-ordination difficulty, memory loss and paralysis.

MSA – Short for Master Service Agreement, an agreement commonly used in the pharma and biotech industry covering the terms of a collaboration between two research groups.

NASH – Short for non-alcoholic steatohepatitis, NASH is a disease condition characterised by the build-up of fat in the liver.

Nephrons – The individual functional units of the kidneys, containing the glomeruli and the tubules.

Nephropathy – Kidney disease or damage.

Nephrotic syndrome – A range of kidney disorders resulting from damage to the glomeruli and characterised by proteinuria. Focal Segmental Glomerulosclerosis is a nephrotic syndrome disorder.

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

Orphan Drug – A drug that benefits less than 200,000 potential patients in the US. Orphan Drug designation provides tax benefits as well as market exclusivity in both Europe and the US.

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.

Podocytes – Cells in the Bowman's capsule that wrap around the glomeruli.

Propagermanium (PPG) – An anti-inflammatory 'organometallic' drug derived from the metal germanium. Propagermanium works through blocking the chemokine receptor CCR2. Propagermanium is one part of Dimerix's lead DMX-200 product.

Proteinuria – Abnormal amounts of protein in the urine, the protein in question being albumin.

Receptor-Heteromer Investigation Technology (Receptor-HIT) – Dimerix's technology for identifying GPCR Heteromers. The platform uses BRET to identify GPCRs that interact.

Special Access Scheme – An arrangement with Australia's Therapeutic Goods Administration that allows patients access unapproved medicines on a compassionate-use basis.

Stage – In Chronic Kidney Disease, there are five disease stages as measured by eGFR: Stage 1, eGFR >90 mL/min/1.73 m^2; Stage 2, eGFR 60-89; Stage 3, eGFR 30-59; Stage 4, eGFR 15-29; and Stage 5 eGFR <15.

Statistical significance - The probability, measured by the 'p-value', that an observed outcome of an experiment or trial is due to chance alone. Generally, p-values below 0.05 are taken as markers of statistical significance.

STNx – A rat model of Chronic Kidney Disease in which the rat is 'subtotally nephrectomised', that is, most but not all (generally five-sixths) of its kidneys are removed. STNx is considered the 'gold standard' animal model for CKD because typically humans can lose >80% of kidney function before feeling sick. Also, the model is not associated with diabetes or inflammation, which can complicate the picture in terms of tracking kidney function.

Tubule – The vessel which carries glomerular filtrate out of the kidneys.

Appendix II - Dimerix's IP position

Dimerix's core intellectual property is covered by two patent families:

- ***Detection system and use therefor***, WO/2008/055313, priority date 10 November 2006, invented by Kevin Pfleger, Ruth Seeber, Heng Boon See and Karin Eidne
  This patent family covers the Receptor-HIT platform. It was granted in Europe as EP 2 080012 in March 2013 while two US patents have been granted – No. 8,283,127 (October 2012) and No. 8,568,997 (October 2013).

- ***Combination therapy***, WO/2012/094703, priority date 11 January 2011, Invented by Kevin Pfleger, James Williams and Liddy McCall
  This patent family covers the combination of Irbesartan and Propagermanium in the treatment of kidney disease. US patent 9,314,450 was granted in April 2016.

Appendix III – Dimerix's Capital structure

		% of fully diluted	Note
Ordinary shares, ASX Code DXB (million)	1,473.6	88.8%	
Unlisted options (million)	111.7	6.7%	Average exercise price 1.2 cents, average expiry date 03-Aug-2017
Milestone shares	75.0	4.5%	Issued when Dimerix gains ethics approval for a clinical trial in a second indication.
Fully diluted shares	1,660.3		

Current market cap:	A$14.7 million (US$11.3 million)
Current share price	$0.0110
Twelve-month range	$0.005 - $0.013
Average turnover per day (last three months)	3.8 million

Appendix IV – Dimerix's major shareholders

Dimerix currently has only two substantial shareholders:

- **Peter Meurs** (21.5%), formerly Director Development for the iron ore miner Fortescue Metals and before that Managing Director ANZ for the engineering company WorleyParsons. Meurs is currently a General Authority of the Church of Jesus Christ of Latter-day Saints.
- **Dr Martin Blake** (5.8%), a Perth nuclear medicine specialist, through Yodambao Pty Ltd. Blake is Chairman of Resonance Health (ASX: RHT), a company of which James Williams was formerly CEO.

Appendix V – Papers relevant to Dimerix

There are 10 peer-reviewed papers that are relevant to Dimerix:

Ayoub and Pfleger, 2010. *Recent advances in bioluminescence resonance energy transfer technologies to study GPCR heteromerisation,* Curr Opin Pharmacol. 2010 Feb;10(1):44-52. Epub 2009 Nov 10.

- This paper reviews the utility of BRET in identifying GPCR heteromers.

Mustafa and Pfleger, 2011. *G protein-coupled receptor heteromer identification technology: identification and profiling of GPCR heteromers*. J Lab Autom. 2011 Aug;16(4):285-91. Epub 2011 May 31 (full text available for free online).

- This paper reviews the Receptor-HIT technology.

See et. al., 2011. *Application of G protein-coupled receptor-heteromer identification technology to monitor β-arrestin recruitment to G protein-coupled receptor heteromers*. Assay Drug Dev Technol. 2011 Feb;9(1):21-30. Epub 2010 Dec 6 (full text available for free online).

- This paper describes the use of Receptor-HIT in profiling various GPCR heteromers.

Porrello et. al., 2011. *Heteromerisation of angiotensin receptors changes trafficking and arrestin recruitment profiles*. Cell Signal. 2011 Nov;23(11):1767-76. Epub 2011 Jun 25.

- This paper shows the use of Receptor-HIT in characterising the heteromers formed constitutively by angiotensin II receptor subtypes 1 and 2.

Johnstone and Pfleger, 2012. *Receptor-Heteromer Investigation Technology and its application using BRET*. Front Endocrinol (Lausanne). 2012 Aug 22;3:101. eCollection 2012 (full text available for free online).

- This paper is another review of the Receptor-HIT technology.

Mustafa et. al., 2012. *Identification and profiling of novel α1A-adrenoceptor-CXC chemokine receptor 2 heteromer.* J Biol Chem. 2012 Apr 13;287(16):12952-65. Epub 2012 Feb 27 (full text available for free online).

- This paper was the first to report that the alpha-1A adrenergic receptor and CXCR2 formed a heteromer.

Watts et. al., 2013. *Identification and profiling of CXCR3-CXCR4 chemokine receptor heteromer complexes*. Br J Pharmacol. 2013 Apr;168(7):1662-74 (full text available for free online).

- This paper described how Receptor-HIT could identify a heteromer of CXCR3 and CXCR4, thereby characterising a potential new target for autoimmune disease and cancer.

Ayoub et. al., 2013. *Profiling epidermal growth factor receptor and heregulin receptor 3 heteromerisation using receptor tyrosine kinase heteromer investigation technology*. PLoS One. 2013 May 20;8(5):e64672. Print 2013 (full text available for free online).

- This paper showed that the principles of Receptor-HIT could be adapted to identify heteromers of receptor tyrosine kinases. The example given was a characterisation of the EFGR/HER3 heteromer.

Jaeger et. al., 2014. *Biophysical Detection of Diversity and Bias in GPCR Function*. Front Endocrinol (Lausanne). 2014 Mar 5;5:26. eCollection 2014 (full text available for free online).

- This paper reviews various technologies for monitoring proximity and/or binding of GPCRs with other proteins.

Ayoub et. al., 2015. *Functional interaction between angiotensin II receptor type 1 and chemokine (C-C motif) receptor 2 with implications for Chronic Kidney Disease*. PLoS One. 2015 Mar 25;10(3):e0119803. eCollection 2015 (full text available for free online).

- This paper reports the angiotensin II receptor type 1 and CCR2 interaction and shows *in vivo* that this target is druggable in kidney disease.

Gomes et. al., 2016. *G Protein-Coupled Receptor Heteromers*. Annu Rev Pharmacol Toxicol. 2016;56:403-25. Epub 2015 Oct 22.

- This paper is a review of advances in the technologies to identify GPCR heteromers.

Appendix VI – Companies to watch

Company	Location	Code	Market cap (USDn	Web
Opko Health	Miami, Fl.	NYSE: OPK	5,377	www.opko.com
Neurocrine Biosciences	San Diego, Ca.	Nasdaq: NBIX	4,522	www.neurocrine.com
Theravance Biopharma	Dublin, Ireland	Nasdaq: TBPH	1,267	www.theravance.com
FibroGen	San Francisco, Ca.	Nasdaq: FGEN	1,194	www.fibrogen.com
Acceleron Pharma	Cambridge, Ma.	Nasdaq: XLRN	1,151	www.acceleronpharma.com
Retrophin	San Diego, Ca.	Nasdaq: RTRX	619	www.retrophin.com
Omeros	Seattle, Wa.	Nasdaq: OMER	471	www.omeros.com
Mesoblast	Melbourne, Australia	Nasdaq: MESO	423	www.mesoblast.com
Arena Pharmaceuticals	San Diego, Ca.	Nasdaq: ARNA	404	www.arenapharm.com
Trevena	King of Prussia, Pa.	Nasdaq: TRVN	386	www.trevena.com
Organovo	San Diego, Ca.	NYSE MKT: ONVO	359	www.organovo.com
Akebia Therapeutics	Cambridge, Ma.	Nasdaq: AKBA	311	www.akebia.com
ChemoCentryx	Mountain View, Ca.	Nasdaq: CCXI	219	www.chemocentryx.com
Regulus Therapeutics	San Diego, Ca.	Nasdaq: RGLS	178	www.regulusrx.com
Cara Therapeutics	Shelton, Ct	Nasdaq: CARA	159	www.caratherapeutics.com
Galectin Therapeutics	Norcross, Ga.	Nasdaq: GALT	57	www.galectintherapeutics.com
Tobira Therapeutics	South San Francisco, Ca	Nasdaq: TBRA	54	www.tobiratx.com
CymaBay Therapeutics	Newark, Ca.	Nasdaq: CBAY	54	www.cymabay.com

GPCR platform companies

- **Arena Pharmaceuticals.** This company's technology allows GPCRs to be activated without the presence of the natural ligand, allowing new, GPCR-activating drugs to be identified. Arena was the original developer of Belviq, Eisai's selective 5-HT2C receptor agonist for the treatment of obesity. Arena is in Phase II with Etrasimod, an S1P1 receptor modulator for the treatment of ulcerative colitis, and Ralinepag, a prostacyclin receptor for the treatment of Pulmonary Arterial Hypertension.

- **Cara Therapeutics.** This company's DimerScreen platform is designed to specifically and selectively identify molecules interacting with GPCR dimers[105]. The company has used this platform to develop CB845, a kappa receptor agonist now in Phase III in postoperative pain and in uremic pruritus, the chronic itchiness that dialysis patients are often afflicted with.
- **Omeros**. This company was originally built around a platform called PharmacoSurgery designed to identify combinations of already approved drugs where the combination, used peri-operatively, can pre-empt potential complications of surgery. The first product from this platform, called Omidria, gained FDA approval in mid-2014 for use in eye surgery. Beyond PharmacoSurgery, Omeros is also a leader in the search for GPCR-targeting drugs, with a library of small molecules that it uses to fish for 'orphan GPCRs' (ie those where the ligand is unknown). The company has, however, yet to take a novel GPCR-targeting drug into the clinic.
- **Trevena**. This company, which counts Robert Lefkowitz as a co-founder, has been built on a platform for the identification of 'biased' ligands to GPCRs, where the bias is for ligands that work through downstream signalling pathways that are beneficial to disease treatment, and against those pathways that would be adverse. Trevena is in Phase III with Oliceridine, a mu-receptor modulator indicated for the management of moderate-to-severe acute pain. This compound was granted Breakthrough Therapy Designation by the FDA in February 2016. The drug retains the analgesia properties of the opioids but avoids pathways that can promote respiratory depression and gastrointestinal dysfunction.

Companies working on new kidney therapeutics

- **Acceleron Pharma.** This company, whose focus is drugs that work by targeting TGF-β (like Fibrotech, the Shire-acquired company), is in Phase III with Luspatercept for the treatment of β-Thalassemia and myelodysplastic syndromes, and in Phase II with Sotatercept for the treatment of CKD. In each case the thinking is that targeting TGF-β can raise red blood cell counts. Both compounds are partnered with Celgene, with that company having paid Acceleron US$75m with the potential to pay US$367m in milestones for Sotatercept and US$200m for Luspatercept.
- **Akebia Therapeutics.** This company is focused on drugs that can increase red blood cell counts by increasing levels of a protein called hypoxia-inducible factor (HIF). Vadadustat, an inhibitor of hypoxia-inducible factor-prolyl hydroxylase, is in Phase III in CKD, both dialysis-dependent and non-dialysis dependent.
- **ChemoCentryx.** This company, whose focus has been on drugs involving chemokines and chemoattractant receptors, has completed Phase II with CCX140, at a CCR2 antagonist for the treatment of diabetic nephropathy. CCX168, a C5aR inhibitor, is in Phase II for various rare diseases including IgA nephropathy.

[105] The platform works by coexpression of GPCR-G Protein fusions in cells, where one fusion can bind ligand but not activate G Protein, while the other fusion can bind ligand and transmit signal to the G protein but not to the G Protein that it is fused to. If signal is generated by these co-expressed fusions it means they form a heteromer. See Mol Pharmacol. 2004 Jul;66(1):1-7. We believe the Dimerix platform is superior to Cara's because the former doesn't mutate the receptors being examined - Dimerix uses essentially one wild type GPCR and another GPCR with only a tag on the c-terminus. Cara requires generation of non-functional mutations on both GPCRs.

- **CymaBay Therapeutics.** This company, focused on rare diseases in the metabolic area, has completed Phase II with Arhalofenate for gout. The company is in Phase II for MBX-2982, a GPCR-targeting drug that treats diabetes by direct action on beta cells as well through the stimulation of GLP-1 in the gut.
- **FibroGen.** This company, like Akebia, is interested in the therapeutic potential of HIF. Roxadustat, an inhibitor of HIF prolyl hydroxylases, in Phase III for CKD anemia.
- **Galectin Therapeutics.** This company is being built around carbohydrate-based drugs that bind to proteins called galectins, known to play a role in fibrosis. Galectin's GR-MD-02 compound is in Phase II in NASH. The company is evaluating its potential in kidney fibrosis.
- **Mesoblast**. This adult stem cell company, whose lead indications are in GVHD, heart failure and chronic low back pain, has done a great deal of work over the last decade or so on the anti-inflammatory properties of its mesenchymal precursor cells. A Phase II study of these cells in Type 2 Diabetes, where the patients had Stage 3b and 4 CKD as a co-morbidity, saw treated patients report preservation or improvement in GFR[106].
- **Neurocrine Biosciences.** This company, whose research focus is small molecule antagonists to GPCRs, is in Phase III with Elagolix, a GnRH antagonist for the treatment of endometriosis and uterine fibroids. Also in Phase III for a movement disorder called tardive dyskinesia is Valbenazine, a drug designed to cut dopamine release by neurons.
- **Opko Health**. This rapidly emerging mid-stage biotech company has renal disease as one of its core focuses. The company has filed for FDA approval of Rayaldee, a first-in-class vitamin D prohormone treatment for secondary hyperparathyroidism in Stage 3 and 4 CKD patients with vitamin D insufficiency. It is in Phase III with Alpharen, a calcium-free non-absorbed phosphate binder for the treatment of hyperphosphatemia in dialysis patients.
- **Organovo**. This company, based on scaffold-free 'bioprinting' technology originally developed at the University of Missouri–Columbia, is working on functional, three-dimensional tissues that can potentially be implanted or delivered into the human body. At present the target market is researchers needing functional human tissue to experiment with. Kidney tissue was one of Organovo's earliest programmes.
- **Regulus Therapeutics**. This company, one of the pioneers of RNA-based therapeutics (its focus is microRNAs, small naturally occurring non-coding RNAs 20-25 nucleotides in length) is in Phase II in Alport syndrome, an Orphan kidney disease. This product has been partnered with Sanofi's Genzyme unit.
- **Retrophin**. This Orphan Drug developer intends to file for FDA approval in 2017 for the use of a liquid formulation of ursodeoxycholic acid in the treatment of a rare liver disease called primary biliary cholangitis (PBC). The company is in Phase II in FSGS for Sparsentan, a selective dual-acting receptor antagonist targeting endothelin and angiotensin II.
- **Theravance**. This company, whose specialty is multi-valent drugs, got its first commercial product in 2009 with FDA approval of Vibativ, a semi-synthetic derivative of the antibiotic vancomycin used in certain difficult-to-treat infections. The company is in Phase III with Revefenacin, a long-acting

[106] See the company's press release dated 9 June 2015 and headlined '*Positive trial results of Mesoblast cell therapy in patients with diabetes and advanced chronic kidney disease*.'

muscarinic antagonist for the treatment of COPD. TD-0714, an inhibitor of neprilysin potentially useful in cardiovascular and kidney disease, is in Phase I.

- **Tobira Therapeutics**. This company, whose main focuses are liver disease and inflammation, is in Phase II with Cenicriviroc, a dual inhibitor of the CCR2 and CCR5 pathways known to be relevant in both inflammation and fibrosis. The first two indications are NASH and a disease of the bile ducts of the liver called primary sclerosing cholangitis (PSC).