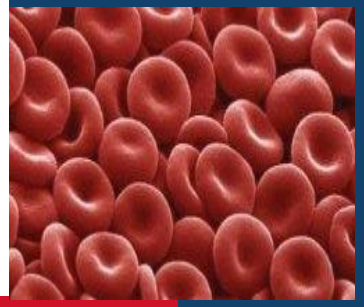
A *collusion of interests*: Hope, hype and science and the shaping of patient's expectations of treatment.



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COSA 2017

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Declarations

- Haematologist/BMT Physician
- Director (Sydney Uni) of *PRAXIS Australia*
- Laboratory Haematologist with *Pathology North*
- Investigator on Phase 1-3 Clinical Trials in BMT and Haematological malignancies
- Investigator on, and recruit to, investigator-initiated and industry-sponsored clinical trials
- No other research, education or consultancy-relationship with Pharmaceutical or Biotech industry.
- Rubbish dancer

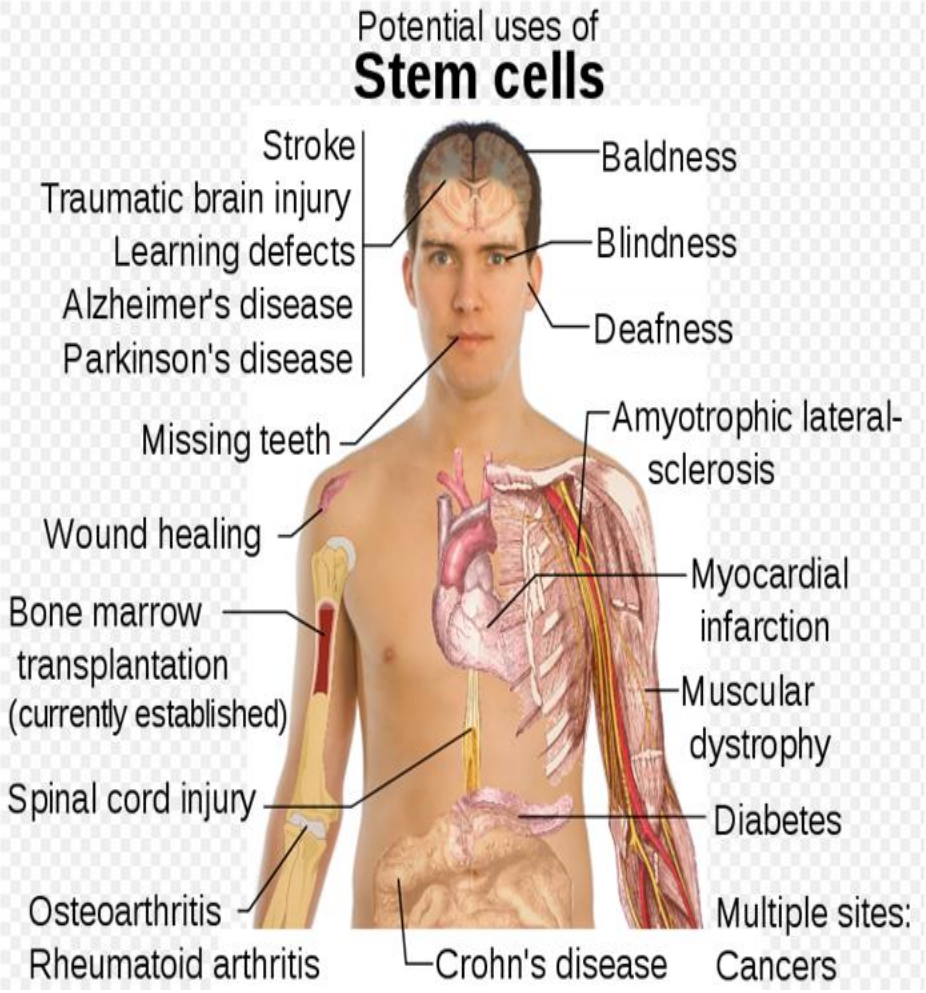
Our Treatments: *Here at Macquarie Stem Cells we are passionate about cellular therapy and the life-changing effects that the treatment can provide.*

http://www.macquariestemcells.com/treatments/benefits-of-stem-cell-therapy/

Potential Uses of Stem Cell Therapy

Stem cells are the key to future healing

The versatility of the stem cell therapy treatment makes it a very valuable scientific medical procedure. Every month scientists are discovering new ways to utilise stem cell therapy and so the boundaries of this medical science continues to be extended. Below are some of the potential uses for stem cell therapy.



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Stem Cell Therapy

Manage the pain associated with osteoarthritis with Stem Cell Treatment

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Effectiveness of New Therapies

Cancer 'breakthrough' could help millions

http://www.9news.com.au/health/2016/10/20/17/03/cancer-breakthrough-could-help-millions

Scientists hail 'triple negative' breast cancer drugs breakthrough

https://inews.co.uk/essentials/news/health/triple-negative-breast-cancer-breakthrough/

Patients "Saved by New Therapies"

'BACK FROM THE DEAD'
Miracle cancer drug SAVES man given two weeks to live

http://www.express.co.uk/life-style/health/672595/Miracle-cancer-drug-saves-man-given-two-weeks-to-live

Miracle drug trial saved woman's life

http://www.9news.com/news/health/miracle-drug-trial-saved-womans-life/196790641

They formed the Beating the Odds Club – melanoma sufferers told they could die within six months but who have defied the odds

http://www.adelaidenow.com.au/lifestyle/health/they-formed-the-beating-the-odds-club--melanoma-sufferers-told-they-could-die-within-six-months-but-who-have-defied-the-odds/news-story/05abb890dbbe85b9e01b73283c471da5

- **Idelalisib is revolutionary and ‘melts away’ cancer**
- **Venetoclax is like taking Panadol**
- **And drug after drug is a ‘miracle cure’**

Difficulties Accessing New Therapies

Cancer drug costs force our children into life-and-death stalemate

http://www.heraldsun.com.au/news/victoria/cancer-drug-costs-force-our-children-into-lifeanddeath-stalemate/news-story/e185e430b67c474e7c8782d49ed6849d

Jess Pereira's cancer nightmare before Christmas

http://www.news.com.au/lifestyle/health/health-problems/jess-pereiras-cancer-nightmare-before-christmas/news-story/d274c7577b12c2e9b317863e1d470673

Aussies patients denied funding for 30 life saving cancer drugs

Source: http://www.news.com.au/lifestyle/health/health-problems/aussies-patients-denied-funding-for-30-life-saving-cancer-drugs/news-story/b2d611942c6f6b2b497030288db951a6

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Dying mum fights for life-prolonging drugs the NHS won't fund due to cost

http://www.dailyrecord.co.uk/news/dying-mum-fights-life-prolonging-8245336

Company denies drug to dying child

http://edition.cnn.com/2014/03/10/health/cohen-josh/

Mum with breast cancer's desperate plea for new drugs to be funded: 'Please don't give up on us'

https://www.tvnz.co.nz/one-news/new-zealand/mum-breast-cancers-desperate-plea-new-drugs-funded-please-dont-give-up-us

Rhetoric around new medicine and unfunded medicines

- **Positive descriptions of new therapies**
  - "Miracle", 'Miracle drug", "Breakthrough", "innovative", "potential cure" and "wonder drug"
  - "Lymphoma melts away"

- **Rich narratives of patients denied access**
  - Denial of treatment described as "cruel", a "death sentence" and a "time bomb"
  - Patients are "angry", "abandoned", "anxious" and "fearful" of what could happen if they don't receive treatment – the treatment that will, most definitely, cure them.

Patients live in a rhetorical sea that speaks only of benefit

And while for some patients, in some situations, with some drugs – the results are extraordinary – and new treatments revolutionary – that is not always the case.

Young mother with lymphoma dies of pneumonia while on idelalisib

Simon's lymphoma progresses on venetoclax

'It just came from nowhere!'

Patient with recurrent Hodgkin Lymphoma dies of Grade IV aGvHD after receiving PD1-inhibitor!

Outline

- **This is not a rant against stem cells**
- **This is not a rant against new therapies or immunotherapies**
- **This is not a rant against industry**

› **This is a cautionary note that in our (understandable) enthusiasm for new therapies and for early access to new therapies we need to ensure that we don't harm patients through creation of unrealistic expectations or inappropriate hope**

› **Examine where expectations may arise from (outside the clinic), whether there is a problem and what should be done about it.**

Media and health influence

- More than 50% of Australians and US citizens report following health news closely
- General public gets most of its information about science from the mass media
- Cochrane Review (2002) has demonstrated strong and consistent impact of media on health service utilisation
- Media (often) more effective than public health campaigns
- Media influences behaviour and expectations of consumers, patients, clinicians and scientists
- Many studies shown impact of media reporting on testing, requests for prescriptions, prescriptions, ED presentations and diagnoses independent of prevalence of disease and (in some cases) evidence to support the test or therapy.
- **Media often blamed for misreporting, distorting and exaggerating research findings and health information**

So where does the media get their information about medicine from?

Investigative Journalism?

- Ideal but……
- Collapse of traditional business models of media
- Rise of social media in creating ‘news’
- Gutting of conventional news media (Fairfax, ABC)
- Loss of health and scientific expertise in journalism
- Loss of time (24-hour news cycle)
- Uncertain standards of on-line news media re health and science – with notable exceptions - *Croakey, the Conversation*

- Research (abstracts)
- Conference abstracts
- Press Releases from Institutions and Researchers
- Pharmaceutical and biotech industry

Research Reporting

- Data doesn't 'speak for itself'
- Interpreted and communicated
- 'Spin' common (reporting that emphasises the beneficial impact of something) – esp in abstracts (20-45% of RCTs)
- **Titles** simplistic and attention grabbing
- **Abstracts often don't align with results and contain spin**
- **Selective reporting of outcomes**
  - Within-group comparisons
  - Subgroup analyses
  - Secondary outcomes
- **Reporting of non-statistically significant results as demonstrating equivalence in treatment effectiveness or lack of difference in AEs/SAEs.**
- **Publication bias**

- Misalignment of abstracts with research results and ‘spin’ in abstracts even more of a problem because:
- Many full-text papers still behind firewalls (so only abstract read)
- Abstracts presented at conferences
- Doctors only read title, abstract and source (and sometimes author)
- Abstracts – and abstracts with spin – shown to influence behaviour and prescribing

Conference Abstracts

- Not peer-reviewed
- Often don't lead to publication (30-70%)
- Create influence on audience
- Influence prescribing
- Create media interests
- Reported in mass media
- Increasingly being used as an 'acceptable but lower' form of evidence to guide prescribing

Press Releases and News Coverage

- **Press Releases:**
  - Promote institution
  - Promote researchers
  - Promote 'impact' of research
  - Promote track record of researchers and increase possibility of further research grants
  - Promote citation of publications

- **BUT – quality of media reports questionable – often inaccurate and unbalanced**
- **Why?**

- **Press Releases**
- 30-50% exaggerate importance of findings, causality, inference etc
- 40-50% contain no caveats re meaning, validation, generalisability
- 30% contain quotes that overstate research

- **Where Press Releases contain exaggeration:**
- 1. **News outlets contain similar exaggeration** (60-90% correlation)
- 2. **Exaggeration explained by:**
  - **research publication itself,**
  - **quotes from researchers and**
  - **press office**

- Yavchitz et al. *Plos Medicine* 2012
- Sumner et al. *BMJ* 2014
- Beijers et al BMJ Open 2017
- Boutron et al. JCO 2014
- Boutron et al JAMA 2010

Industry and the Media

- As the capacity of the media has reduced and advertising revenue has reduced - the role of industry has increased
  - Press Releases
  - Video/audio news releases (VNRs): story, images, patient, expert, clinician – high quality
  - Resources for journalists
  - Access to medical and scientific experts
- ALSO
  - Sponsor education, conference travel and awards
  - Gifts
  - Employ journalists as consultants

Commerce in research

- >80% of all clinical research in US and Australia is sponsored by the pharmaceutical industry
- >80% of professional organizations and journals are sponsored by, or receive advertising revenue from, the pharmaceutical industry
- >75% of patient/advocacy groups are supported by the pharmaceutical industry

Implications

- Distortion of research agenda (90/10 divide)
- Distortion of evidence on efficacy (more often favourable)
- Distortion of evidence on cost-effectiveness (more favourable)
- Distortion of research question: no head-to-head studies
- Distortion of methods in medicine (move from superiority to non-inferiority trials)
- Selective reporting of data favourable to product
- Loss of researchers independence and integrity
- Creation of multiple ties and conflicts of interest
- Increased secrecy in medicine and research
- Delay or non-publication of key findings for commercial reasons (Cox-2 inhibitors, SSRIs)
- Erosion of public trust in research, medicine, HCPs and primacy of patient needs.

Medical journals and Pharma

- *Journals have devolved into laundering operations for the pharmaceutical industry.* Richard Horton, Lancet
- *Journals have been co-opted by industry*. Marcia Angell, NEJM
- *Medical journals are an extension of the pharmaceutical industry*. Richard Smith, BMJ.
- *There is a cycle of dependency between journals and the pharmaceutical industry*. PLoS Editors.

…….it will probably take years before we can determine the extent to which the evidentiary water supply has become polluted in the last few decades as a result of commercial bias (Brody, 2005)

Collectively – both the data around new therapies and the rhetoric around new therapies (from researchers, research institutions, the media and social media) has created an 'Access Imperative'

Has progress been miraculous?.....Sometimes

- TKIs in CML
- PD-1 Inhibitors in Melanoma
- CAR-T in just about everything (potentially)
- BUT:
- Innovative cancer drugs have improved 5-year survival over 21 years by 4.8% in Australia (approx. 0.2% p.a.)
- Median survival improvement for new cancer drugs for solid tumours = 2.1 months.

Accelerating access to medicines

- **GOOD reasons to speed access to medicines** – patients are desperate, some groups of patients are left behind, regulatory and subsidisation processes may be too slow and inflexible and we want to provide the best possible care.
- **So worldwide:** Right-to-Try legislation, accelerated approval schemes, coverage with evidence development schemes, special access schemes, specific programs for specific drugs etc etc
- BUT accelerating access is not unproblematic:

Compromises in standards of evidence for new therapies

- The FDA now approves 70% of new cancer medicines based on surrogate end-points. 50% of these have subsequently shown no improvement in survival. (Kim et al, JAMA 2015)
- Pivotal cancer drug trials used for FDA approval accept lower evidence:

  -least likely to be double blinded (only 27.3% vs 78%).

  -least likely to have a comparator (only 47% vs 86%).

  -median of 266 patients per trial.

  -median duration of trial 18.4 weeks (Only 30% longer than 6 months).

Compromises in standards of evidence for accelerated therapies

- Medicines approved via accelerated access programs:
- More likely to be withdrawn from the market
- More likely to receive a ‘black box’ AE warning eg gemtuzumab for AML
- Often are shown to be ineffective (less than 40% offer an advantage over existing therapy and insufficient data to assess another third)

Evidence for new therapies and the rhetoric surrounding new therapies also – inevitably – influences the ways that patients may regard treatment, the conversations that they have with clinicians and the treatments they are given

Decision-making and consent to treatment

- Consent is not about forms – it is a process, an iterative discussion.
- Large volume of research that shows that patients over-estimate benefit and minimise risk.
- Hope is supreme, uncertainty a reality and fear ever present
- Illness (and hospitals) create vulnerability and make voluntary decision-making (nigh on) impossible
- **Benefit = number + value** (even a remote possibility of benefit may be sufficient to determine a decision or request if valued)
- So understandings, hopes and expectations are important.

So what can be done?

- **If some of blame for exaggeration lies with researchers and institutions?**
  - Don’t do it!
  - Less hubris – more critique and better peer review
  - Consensus re standards of statistical significance
  - Structured reporting of research
  - Formalise structure of press releases
  - Challenge culture of universities, funding bodies
- **Media**
  - Create better firewalls, regulation rather than self-regulation?
  - COI registers (if RACP cannot be convinced – what chance media??)
- **Industry**
  - Too little time!

So what can be done?

- **In the clinic and at the bedside – plenty**
- Acknowledge democratisation of knowledge – benefits and harms
- Open relationship
- Declaration of interests
- Honesty re limits of data, efficacy and adverse events
- Genuine discussion of alternatives – even where these are death
- Second opinions where appropriate
- Assistance making sense of data and ‘noise’ and in translating research results to the patient
- Promise of *presence*

Acknowledgements

- **NHMRC Project Grant Team:**
- Wendy Lipworth, Ian Olver, David Isaacs, Paul Komesaroff, Narcyz Ghinea, Glenn Salkeld

- **ARC Discovery Grant Team:**
- Simon Chapman, Chris Jordens, Wendy Lipworth, Bronwen Morrell, Rowena Forsyth

- Jessica Pace