NHS Blood and Transplant

Clinical Applications of Mesenchymal Stromal Cells

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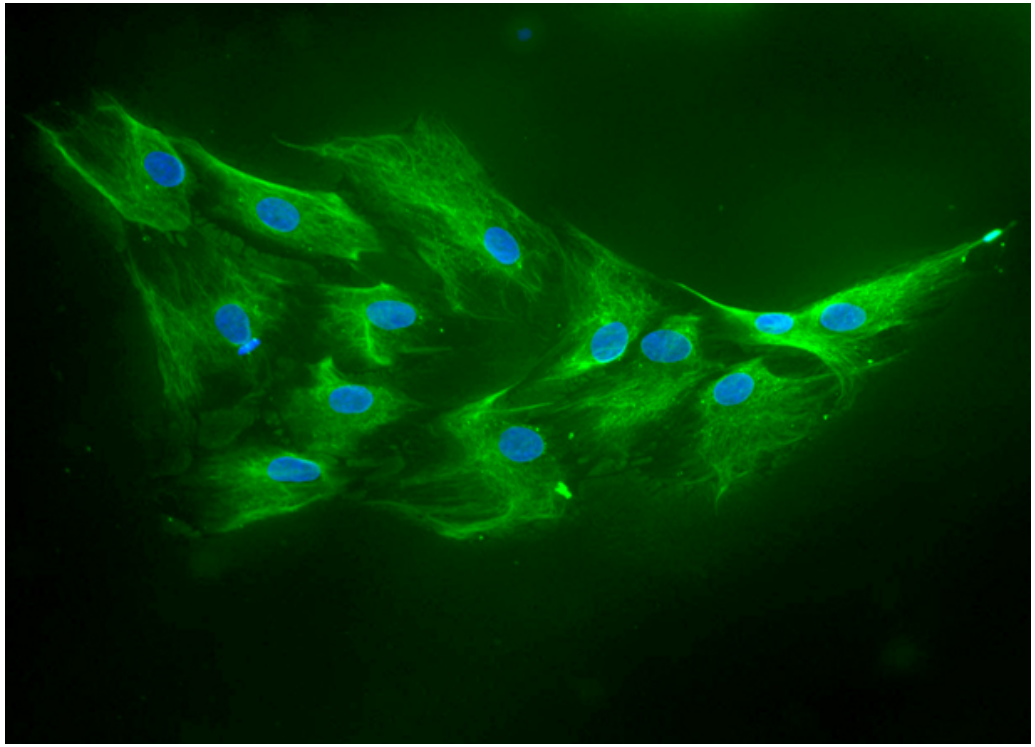
NHS Blood and Transplant, Oxford
John Radcliffe Hospital

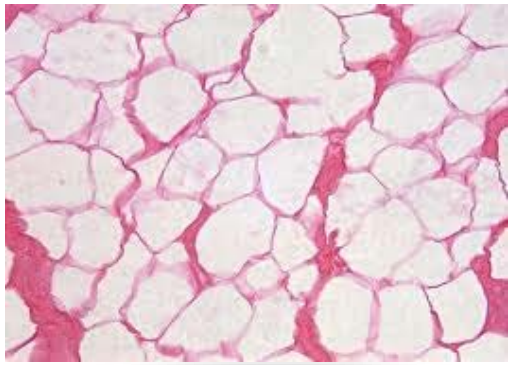
Mesenchymal Stromal Cells (MSC)



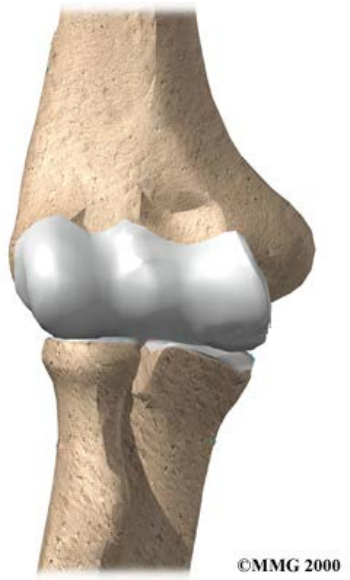
Fibroblastic, plastic adherent
Don’t express haematopoietic markers (eg CD45)
Do express CD73 and CD90
Low levels of HLA Class I, no Class II unless stimulated with IFNγ

Mesenchymal Stromal Cells (MSC)

Bone



Fat

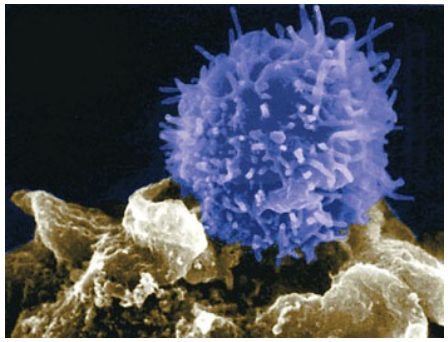


Cartilage

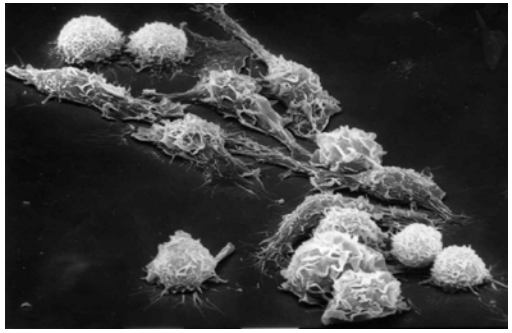
Images: edc2, sciweb, MMG

MSC are Immunosuppressive

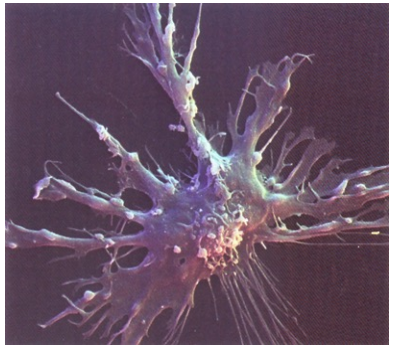
T Lymphocytes



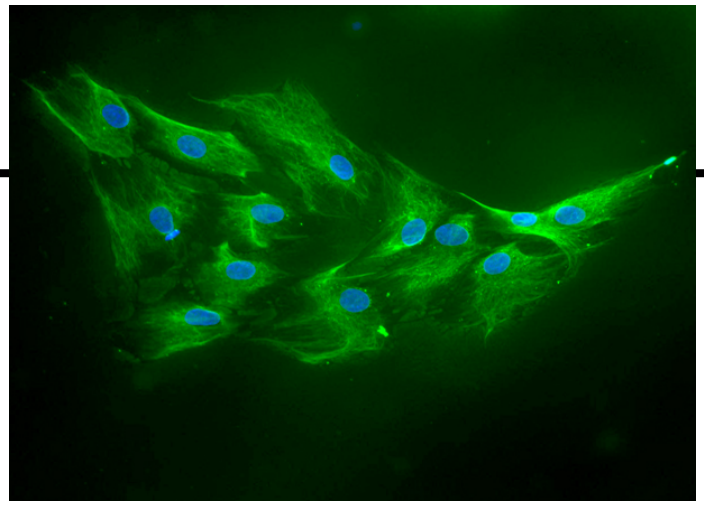
B Lymphocytes



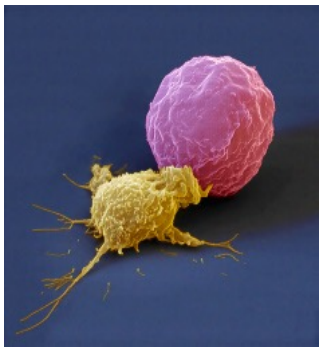
Dendritic Cells



Monocytes



NK Cells



MSC Clinical Trials

700 clinical trials registered
- most involve the immune and trophic properties of MSC

Graft-versus-Host Disease
Solid organ transplant rejection
Crohn's disease
Multiple Sclerosis
Diabetes I
Lupus
.... Stroke, Heart failure

Mostly allogeneic (time, cost, clinical)

Mostly BM, increasingly adipose or cord-derived

Injected IV, 1-2 $x10^6$ cells / kg → 10^9 / patient

Grown in FCS, increasingly platelet lysate

No adverse events attributed directly to MSC

Stem cells Thursday 16 March 2017

Three women with eye disease blinded by unproven stem cell treatment

Florida case an example of growing 'wanton misapplication of cellular therapy', says dean of Harvard Medical School

Each woman was injected in both eyes with a cell preparation derived from her own fat tissue. "It's very alarming to us as clinicians that somebody would do this to both eyes at the same time," said Albini. He said all suffered detached retinas.

Many stem cell clinics argue they aren't subject to regulation by the US Food and Drug Administration (FDA), which oversees most research in people.

The federal database where the Florida clinic listed a study is called ClinicalTrials.gov. Albini said a listing there was no guarantee that a study was legitimate.

The COCHRANE Library: Systematic Review

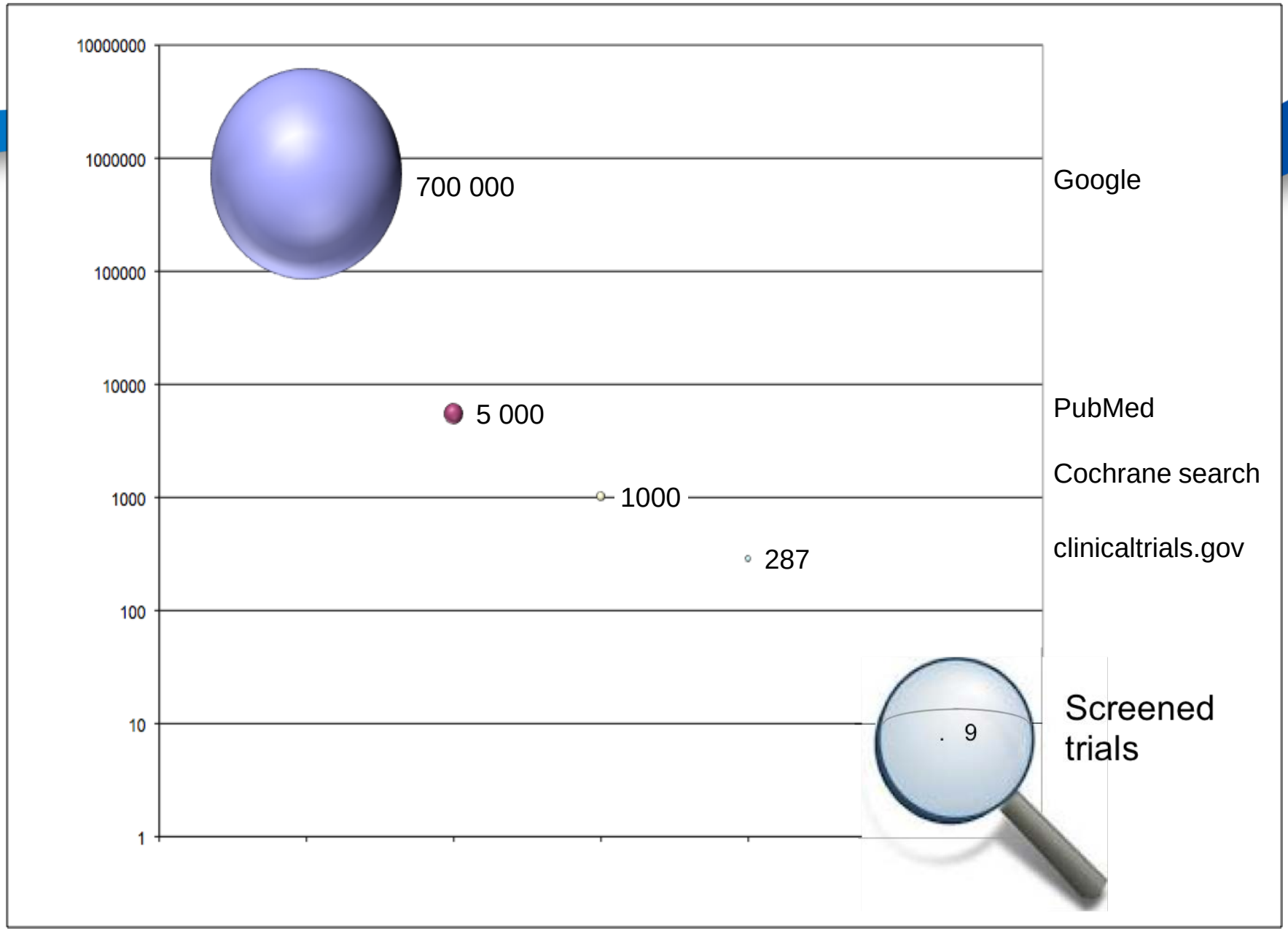
"Mesenchymal stromal cells (MSC) for treating immune-mediated inflammation post-transplantation and in autoimmunity"

Fisher S, Cutler A, Brunskill S, Stanworth S, Navarrete C, Girdlestone J

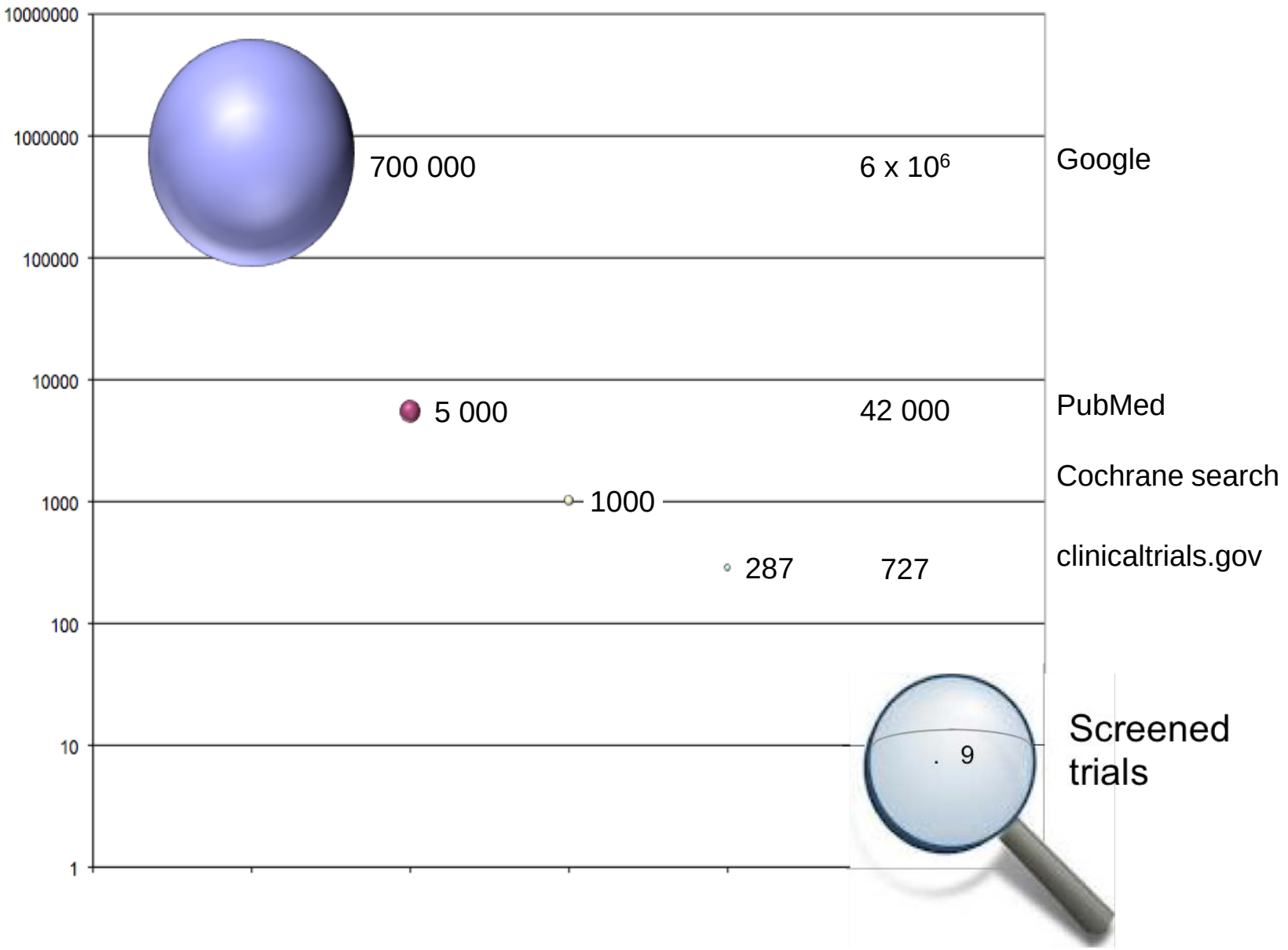
Intervention Protocol 16 May 2012 DOI: 10.1002/14651858.CD009768

Randomised, controlled trials

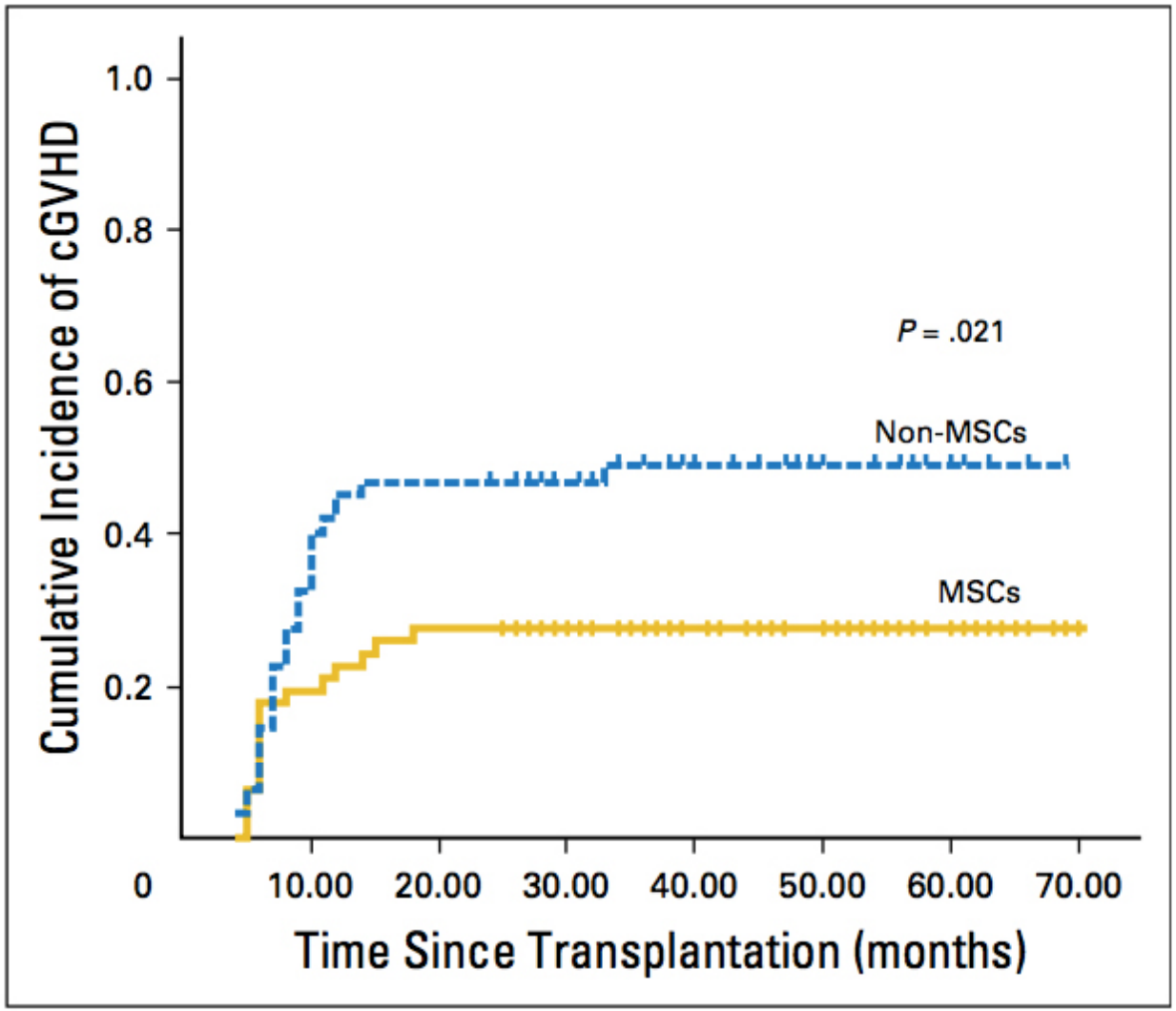
MSC Database Hits



MSC Database Hits



Prophylaxis for Chronic GvHD



62 / arm

Gao et al. J Clin Oncol. 2016 34:2843-50

THE LANCET 388 (2016) 1281-1290

Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial

Liposuctate from healthy donors, expanded in FCS

212 patients were randomly assigned:

'A significantly greater proportion of patients treated with Cx601 versus placebo achieved combined remission in the ITT'

53 of 107 [50%] *vs* 36 of 105 [34%]

97·5% CI 0·2–30·3 (p=0·024)

Why are SCI / Transfusion Labs involved?

- Storage of frozen product / placebo
- Issue of product – thawing, washing, pooling, blinding, transport

Athersys / Catapult	Phase I/II	MultiStem for Acute Respiratory Distress Syndrome
Cynata	Phase I	iPS-derived MSC for aGvHD

NHSBT Cell Therapies 2017/18

Product and indication	Partner(s)	Funder
Mesenchymal stem cells for primary sclerosing cholangitis[1] (MERLIN trial)	University of Birmingham Orbsen Therapeutics	EU Framework Programme 7
Mesenchymal stem cells to create a 'cell bandage' for cartilage repair	Azellon Cell Therapeutics University of Liverpool Cell Therapy Catapult	Innovate UK
Mesenchymal stem cells for diabetic kidney disease (NEPHSTROM trial)	University of Leiden Ludwig-Maximilians University Orbsen Therapeutics	EU Horizon 2020
Mesenchymal stem cells for acute respiratory distress syndrome (REALIST 2)	Orbsen Therapeutics	Wellcome Trust
Cord MSC for Renal Transplant	**Oxford University Hospitals**	**NHSBT**

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‘Our MLC–based product manufacturing and distribution process generally involves five major steps:

• Acquire bone marrow from healthy adults with specific regulatory defined criteria, which is accompanied by significant laboratory testing to establish the usability of the donated tissues.

• Create master cell banks by isolating MLCs from the donated bone marrow and performing a preliminary expansion to create master cell banks. Each individual master cell bank comes from a single donor.

• Expand to therapeutic quantities by growing cells in the master banks to produce therapeutic quantities. This process that can yield thousands of doses per master cell bank, with the ultimate number depending on the dose for the respective product candidate being produced.

• Formulate, package and cryopreserve

• Distribute .. To treatment centers.’

OrbsenTherapeutics

- ‘Orbsen has identified a marker protein* as a tool for selecting therapeutic stromal stem cells from the mixture of cells residing in the bone marrow, umbilical cord, or fat tissue. Antibodies to this marker recognize a protein on the stromal cells’ surface and enables the isolation of a clearly defined population of nearly 100 percent pure stromal cells from the tissue of human donors. These selected cells can be expanded in culture to form many therapeutic doses and can be used allogeneically in patients (i.e. one donor, multiple unrelated recipients). ’

*CD362

Athersys
inc.

- ‘ **MultiStem Product Profile**
- Cell therapy product based on **patented (MAPC®) technology**
- Developing for **"off-the-shelf" administration** - no tissue matching needed
- **Large scale production potential**
  (e.g., millions of doses from each donor)
- **Long storage life** - can be kept frozen for years
- **Consistent safety profile**
- **Promotes healing and tissue repair** through **multiple mechanisms of action**
- Not a permanent transplant - **cells cleared** from the body over time (like a drug)’

MAPC: Multipotent Adult Progenitor Cell

- “The Cymerus™ technology utilises induced pluripotent stem cells (iPSC) and a recently identified precursor cell, known as a mesenchymoangioblast (MCA), to achieve economic manufacture of cell therapy products, including mesenchymal stem cells (MSCs), at commercial scale.”

- “Cynata expects to be able to source all of the cells it will ever need from a single donor.”

“Cynata has received regulatory approval to conduct the first Phase 1 clinical trial with Cymerus™ MSCs in patients with graft-versus-host disease (GvHD).”

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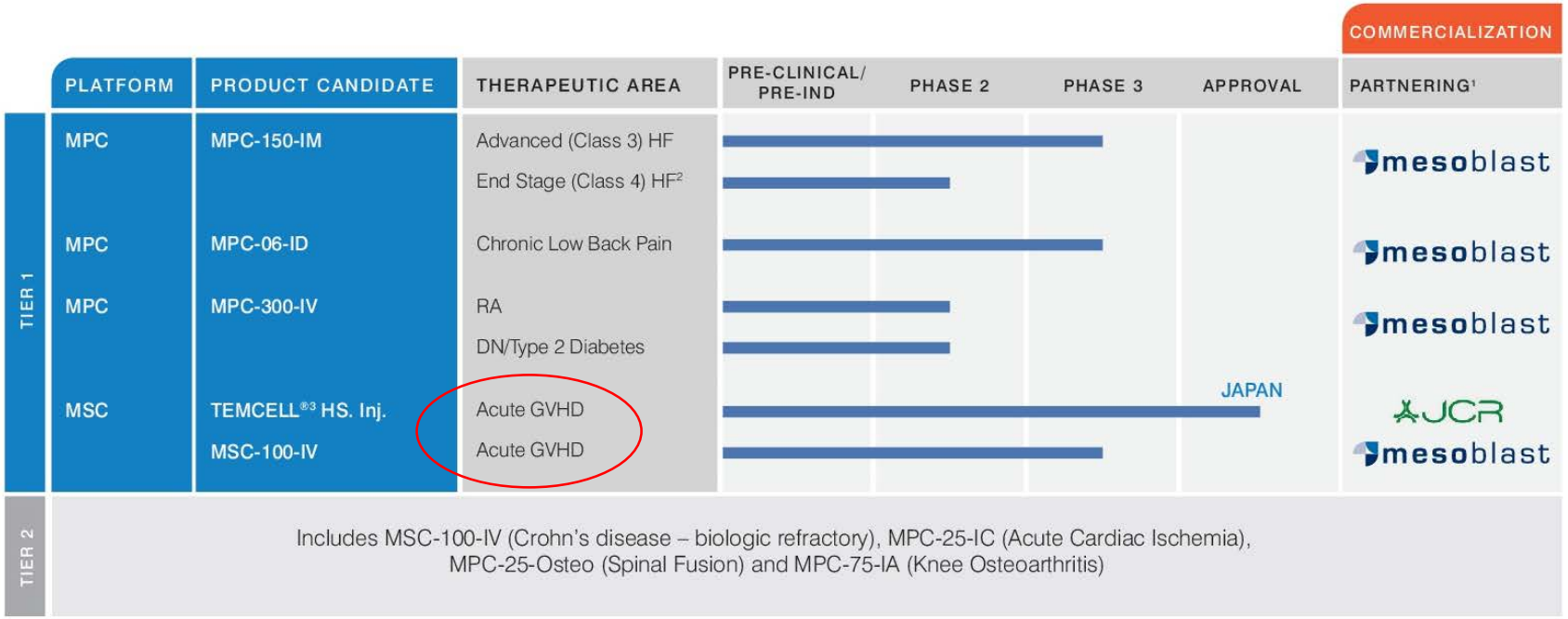

This chart is figurative and does not purports to show individual trial progress within a clinical program. For product registration purposes, Phase 3 programs may require more than one trial. Tier 1 programs represent our lead programs where we focus the majority of our time and resources. Tier 2 programs are also in development and may advance to Tier 1 depending on the merit of newly generated data, market opportunity or partnering options.

1. On December 22, 2016, Mesoblast Ltd. entered into an equity purchase agreement with Mallinckrodt Pharmaceuticals for ~US$ 21.7m to exclusively negotiate a development and commercialization partnership for rights to GVHD and Chronic Low Back Pain outside of the Chinese and Japanese markets.
2. Clinical trial is fully funded by the National Institutes of Health (NIH).
3. TEMCELL® HS. Inj. is a registered trademark of JCR Pharmaceuticals Co., Ltd.

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’The Japanese Government’s National Health Insurance set reimbursement for TEMCELL at ¥868,680 (approximately US$7,700) per bag of 72 million cells.

In Japan, the average adult patient is expected to receive at least 16 or up to 24 bags of 72 million cells. On this basis, Mesoblast expects a treatment course … to be reimbursed at a minimum of … $123,000 or up to $185,000.’

THE AUSTRALIAN

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‘Mesoblast chief executive Silviu Itescu told a recent conference of Japanese business leaders in Australia that the company would apply for early approval under Japan’s new streamlined clinic trial regimen for its chronic heart failure treatment.’

‘Under the changes introduced by Japan in 2014 to accelerate approval for stem cell therapies, companies can use the results of phase two trials in the US with Japanese bridging studies to achieve conditional approval to market the product in Japan. A positive phase-three trial will lead to full approval.’

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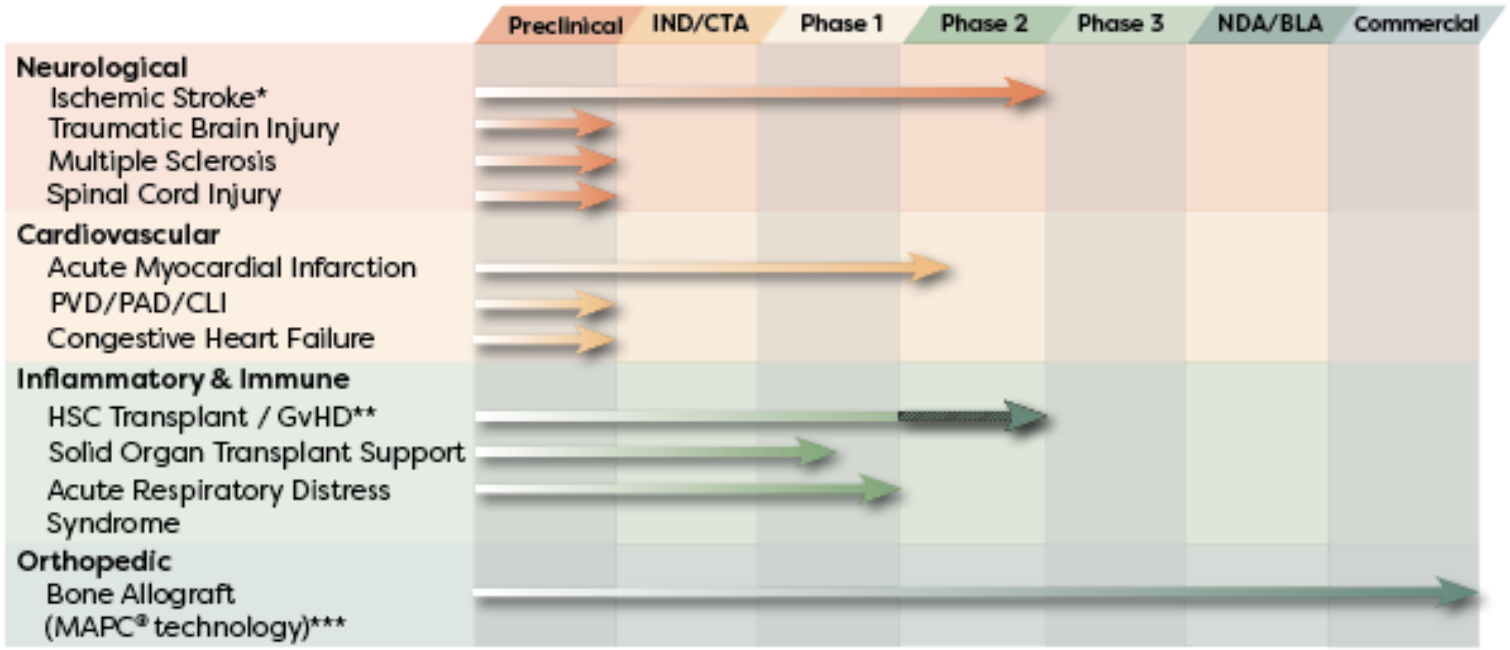

* MASTERS-2 Phase 3 pivotal study under Special Protocol Assessment by the FDA; Also, in partnership with Healios, Phase 2/3 clinical trial commenced in Japan under new accelerated regulatory framework and received priority review designation from PMDA.

** Program authorized for Phase 3 pivotal study under Special Protocol Assessment by the FDA. Program awarded Orphan Drug status by FDA and EMA, and Fast Track by FDA.

*** Partnership with RTI Surgical, Inc.

Release Criteria

Mandatory Infectious Disease markers

Mycoplasma

Endotoxin

Viability

Karyotype

- Positive : CD73, CD90, CD105
- Negative : CD34, CD45, HLA-DR

Potency ?

Release Criteria

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Potency ?

Trilineage differentiation

– relevance for immunoregulation?

‘The mesenchymal stromal cells dilemma—does a negative phase III trial of random donor mesenchymal stromal cells in steroid-resistant graft-versus-host disease represent a death knell or a bump in the road?’

J. Galipeau *Cytotherapy* (2013) 15: 2-8

I propose that at least five MSC parameters are worthy of study and further translational development:

(i) donor selection based on mechanistically defined potency assays
(ii) analysis of early versus late passage,
(iii) analysis of MSC functionality
(iv) analysis of senescent cell content
(v) analysis of pre-existing and acquired alloimmunization to MSC products and impact on transfusion biology.

Potency Assays

If MSC are used primarily for treating immune-related problems, why are no immune assays being used?

(What potency assays does JACIE want for DLIs?)

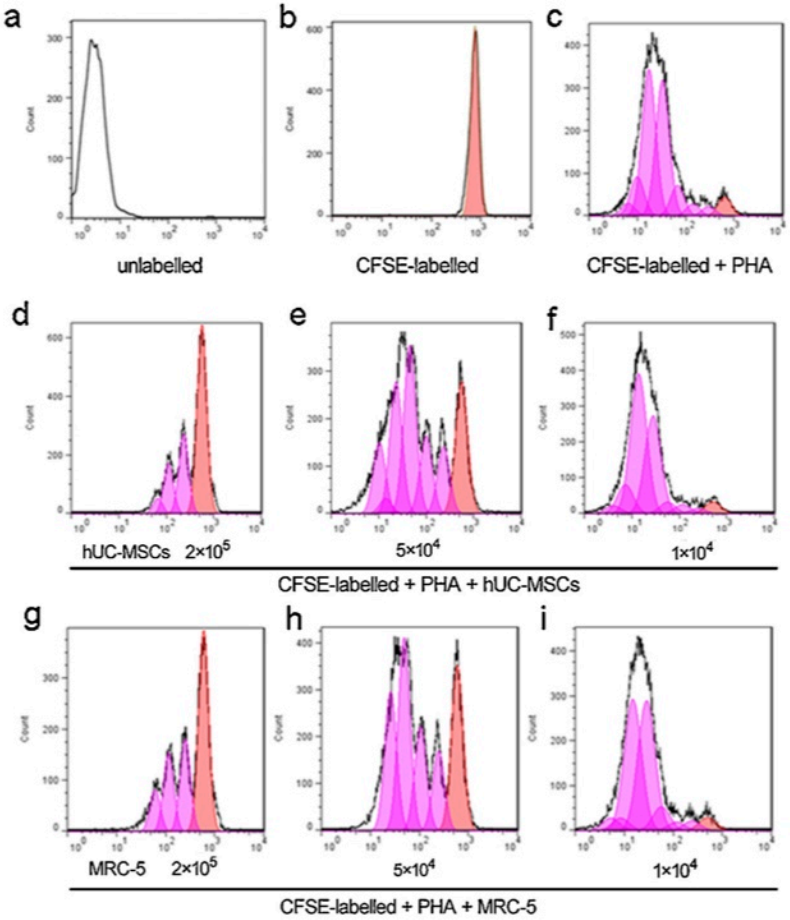
It’s hard enough to standardise CD34 counting between (& within) labs, so developing functional immunosuppression assays is a challenge.

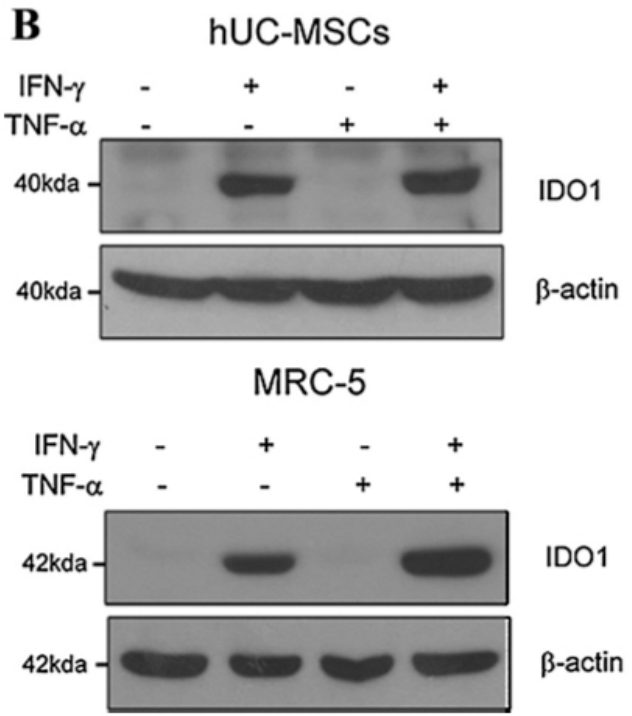
Transcriptome and / or proteome as surrogates

‘Human diploid MRC-5 cells exhibit several critical properties of human umbilical cord-derived mesenchymal stem cells’

Zhang et al. *Vaccine* (2014) 32: 6820-6827

MRC5 are Immunosuppressive





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World Health Organization Reference Cell Banks (RCBs)

WHO MRC-5 RCB

This RCB was prepared in a qualified cleanroom environment and subjected to specified quality-control testing endorsed by the ECBS.

The principle of establishing RCBs under WHO auspices is one that offers potential solutions to future challenges for the development of vaccines and biotherapeutics in developing regions.

MSC with Enhanced Properties

- A simple incubation with immunosuppressive drugs can enhance their potency in vitro and in vivo.

- Other groups have shown a similar adsorption of anti-cancer and antibiotic drugs

- Using standard ISDs should hopefully lower the barriers to developing a potential therapeutic cell product

Girdlestone (2016) Immunotherapy 8:1405-1416

Summary

NHS Blood and Transplant

- MSC have immunosuppressive properties in addition to
  their ability to differentiate into connective tissue derivatives

- A large number of clinical trials are underway to test their
  efficacy in a large range of indications

- Stem cell laboratories are well placed to provide support
  for trials (and eventual routine treatments?)

Acknowledgments

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King's College
Giovanna Lombardi

Harefield Hospital
Neil Leaver

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NHSBT Project Grant
Bloodwise
(Leukaemia and Lymphoma Research)

To support filing of a biologic license application to the United States Food and Drug Administration (FDA) for regulatory approval, a 60-patient, open label Phase 3 trial using MSC-100-IV is being conducted as front-line therapy in children with steroid-refractory aGVHD. In November 2016, this trial was successful in a pre-specified interim futility analysis with topline results expected in 2017. Mesoblast plans to broaden the use of its therapy in adult patients with high-risk steroid-refractory aGVHD.

‘Athersys and Cell Therapy Catapult announce grant to support Clinical Development of Stem Cell Therapy for Severe Acute Respiratory Condition.’