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# Patent Analytics on Stem Cell Technologies Underlying Regenerative Medicine

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## FOREWORD

The Centre for Stem Cell Systems at the University of Melbourne is delighted to partner with IP Australia to map the know-how created by stem cell research in Australia and globally, providing clarity on opportunities for stem cell-based inventions that will benefit the Australian public.

Pluripotent stem cells are capable of giving rise to any tissue of the body, enabling the development of novel applications to understand and treat disease. Since 2006, it has been possible to make pluripotent stem cells from any person. Australian researchers were early adopters of the technologies to engineer these *induced pluripotent stem cells* and have since pioneered methods using these stem cells to grow many tissues in the laboratory, including cells of brain, blood, eye, liver, muscle, kidney and immune system.

Australian stem cell research has been supported by substantial funding from the Australian Government since 2003 through the establishment of the Australian Stem Cell Centre, Australia's first Biotechnology Centre of Excellence, followed by the Australian Research Council Special Research Initiative, Stem Cells Australia (2011-2019). Specialist centres in stem cell research were formed in Melbourne (2009 Australian Regenerative Medicine Institute, Monash University; 2016 Centre for Stem Cell Systems, The University of Melbourne) and Brisbane (2016 Centre in Stem Cell Ageing and Regenerative Engineering, The University of Queensland). This 16-year history of research has generated know-how and IP for improved stem cell growth and differentiation, as well as mathematical predictions to fast-track transformation of one cell type to another. This work has laid the foundation of the next generation of research which now uses stem cells to model and treat diseases.

The Centre for Stem Cell Systems at the University of Melbourne was established to bring together the different scientific disciplines needed to progress stem cell research and understand the societal impacts of that research. We foreshadow stem cell technologies that can repair or replace human tissue, be developed for new diagnostics and theranostics, and form the foundation of implantable technologies that will help patients and clinicians monitor and manage chronic disease. Recognition of the IP landscape is an essential consideration if Australia is to capitalise on the next wave of stem cell research.

Professor Christine Wells  
Director  
The Centre for Stem Cell Systems at the University of Melbourne



# CONTENTS

Foreword .....	3
Summary .....	5
Introduction .....	6
Why patent data? .....	6
Patent landscape analysis .....	7
Timeline .....	7
Patent filing destinations .....	9
Applicant origin .....	10
Top applicants .....	11
Collaboration .....	15
Technology analysis .....	17
Stimulation and tissue engineering .....	21
Timeline .....	21
Subcategories of stimulation and tissue engineering .....	22
Top applicants .....	24
Applicant origin and patent filing destinations .....	26
Conclusion .....	27
Appendix A: Definitions .....	28
Patents, applications and publications .....	28
Patent families .....	28
Classification .....	28
Appendix B: Search Strategy .....	29
Data extraction and analysis .....	29
Search strategy .....	29
Appendix C: Technology Analysis .....	30
Appendix D: Patent Status Determination .....	31

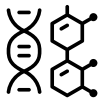
## SUMMARY

This patent analytics report was prepared for the Centre for Stem Cell Systems of the University of Melbourne, and investigates the development of technology relating to mammalian pluripotent stem cells.

Mammalian pluripotent stem cells provide valuable insights into cell biology and differentiation, and are used in disease models, drug development and screening, and regenerative cell therapy. This report includes analysis of innovation in stimulation and tissue engineering with mammalian pluripotent stem cells, an area of particular interest to the Centre for Stem Cell Systems.



**5447 patent families** have been **filed for** mammalian pluripotent **stem cell technology** since 2008.



**591** patent families **relate to stimulation and tissue engineering** with mammalian pluripotent stem cells.



**Kyoto University** is the **top global innovator**, with 172 patent families, and the top global collaborator, with 61 collaborative patent families.



Patent protection is important in mammalian pluripotent stem cell technology, with **96 per cent** of patent families either granted or **with protection** being sought.



**98 per cent** of patent family **relating to stimulation and tissue engineering** with mammalian pluripotent stem cells are either granted or **with protection** being sought.



**Trends demonstrate** that mammalian pluripotent stem cell technology is an area of **continuous growth** over time.



The **United States** dominates as the **largest target market**, with **52 per cent** of global patent filings.



Globally, **Australia is the seventh largest target market**, but Australian applicants rank fourteenth for patent filings in this field. Only 5 per cent of the patents filed in Australia are filed by Australians.



The **University of Queensland is the top Australian applicant** with seven patent families; one of these was filed in collaboration with Griffith University and another with Australian Stem Cell Centre Limited.

## INTRODUCTION

This patent analytics report was prepared for the University of Melbourne, Centre for Stem Cell Systems and investigates the development of technology relating to mammalian pluripotent stem cells.

Stem cell research, a focus of the University of Melbourne, spans research disciplines including synthetic and developmental biology, tissue engineering, bioinformatics, ethics, sociology and law. The Centre for Stem Cell Systems aims to develop excellence and impact in stem cell biology, tissue engineering and stem cell medicine, with three main streams of activity: excellence in stem cell research with a strong research environment and cross-disciplinary stem cell research; development of a training path at undergraduate and postgraduate levels to support growth in the sector; and partnering with government, professional bodies and community advocates to understand the expectations and barriers to delivering stem cell medicine.<sup>1</sup>

Stem cells possess two unique characteristics that distinguish these cells from other cell types. Firstly, stem cells are able to self-renew, meaning they can perpetually create more copies of themselves. Secondly, stem cells have the capacity to differentiate into the many different cell types of the body.<sup>2</sup>

There are three major types of stem cells: embryonic stem cells (ES cells), induced pluripotent stem cells (iPS cells) and adult (tissue) stem cells. ES cells are naturally-occurring pluripotent cells derived from the undifferentiated cells present in early stage embryos. iPS cells are generated by introducing specific reprogramming factors into adult somatic (differentiated) cells to induce pluripotency. These pluripotent stem cells have the capacity to differentiate into all cell types of the body, and

therefore can potentially produce any body tissue/organ. Adult stem cells are found in the various tissues and organs of the human body and serve as a source of new cells for replacing those lost to natural turnover, damage or disease.<sup>3</sup> Adult stem cells are multipotent and can only differentiate into a limited number of specialised cell types that are specific for their organ of origin.

This report has focused on innovations associated with pluripotent stem cells (ES and iPC cells) with an emphasis on their stimulation and their use in tissue engineering applications, areas of particular interest to the Centre for Stem Cell Systems.

### Why patent data?

IP Australia is dedicated to building prosperity for Australia and ensuring that Australians benefit from great ideas. Using patent analytics to provide evidence of innovation trends, we leverage our unique access to IP data, knowledge and expertise to deliver value to the Australian economy.

We use patent information to assess research and innovation. Patent documents must disclose full details of an invention. This means that patent literature shows development in science and technology. Patents also include information about applicant and inventor names, location and technology area. This data is used to measure patent numbers over time, geographical location, collaboration and research impact. More information about the patent system is given in Appendix A.

<sup>1</sup> About the centre, <https://biomedicalsciences.unimelb.edu.au/departments/anatomy-and-neuroscience/engage/cscs/about-us/about-the-centre>

<sup>2</sup> Types of stem cells, <https://www.eurostemcell.org/types-stem-cells-and-their-uses>

<sup>3</sup> CIRIM, stem cell key terms, <https://www.cirm.ca.gov/patients/stem-cell-key-terms>

# PATENT LANDSCAPE ANALYSIS

As a basis for this study, we searched the worldwide patent databases for inventions relating to mammalian pluripotent stem cells. The search also covered cell stimulation treatments, electro-conductive scaffolds and cell self-assembly/scaffold-free aggregation. The Derwent World Patent Index (DWPI) database was the source of data. The search found 5447 unique DWPI patent families (Appendix A: Definitions) published worldwide with a priority date on or after 1 January 2008 when the DWPI database was accessed on the 29 October 2018.

The search used a combination of keywords, International Patent Classification (IPC) symbols and Cooperative Patent Classification (CPC) symbols (the full search strategy is shown in Appendix B: Search Strategy).

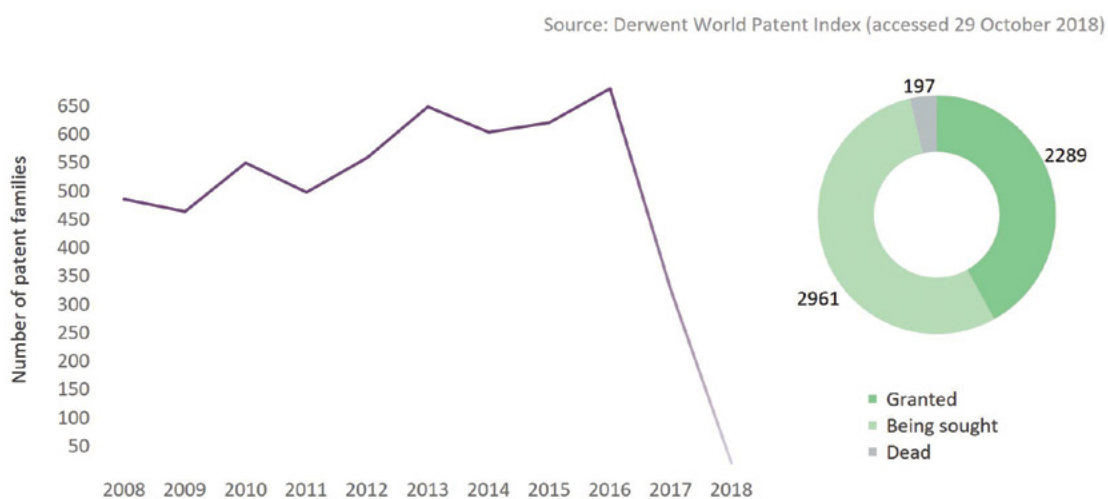
## Timeline

Analysing patent families filed across time shows growth or decline in innovation. Additional in-depth analysis can help understand underlying factors and their correlation to these trends. This can inform strategies around research, development, collaboration and commercialisation. Figure 1 shows the number of patent families by their status and earliest priority year. Patenting activity has slowly increased from 485 patent families in 2008 to a peak of 680 patent families in 2016.

## Status

Figure 1 shows that 5250 (96 per cent) patent families out of 5447 filed since 2008, relating to mammalian pluripotent stem cell technology, are

Figure 1: Patent families relating to mammalian pluripotent stem cells by status and earliest priority year



(Note: data for 2017–18 is incomplete due to a lag in patent publication: the dip in this timeline reflects incomplete data rather than a declining trend in applications)



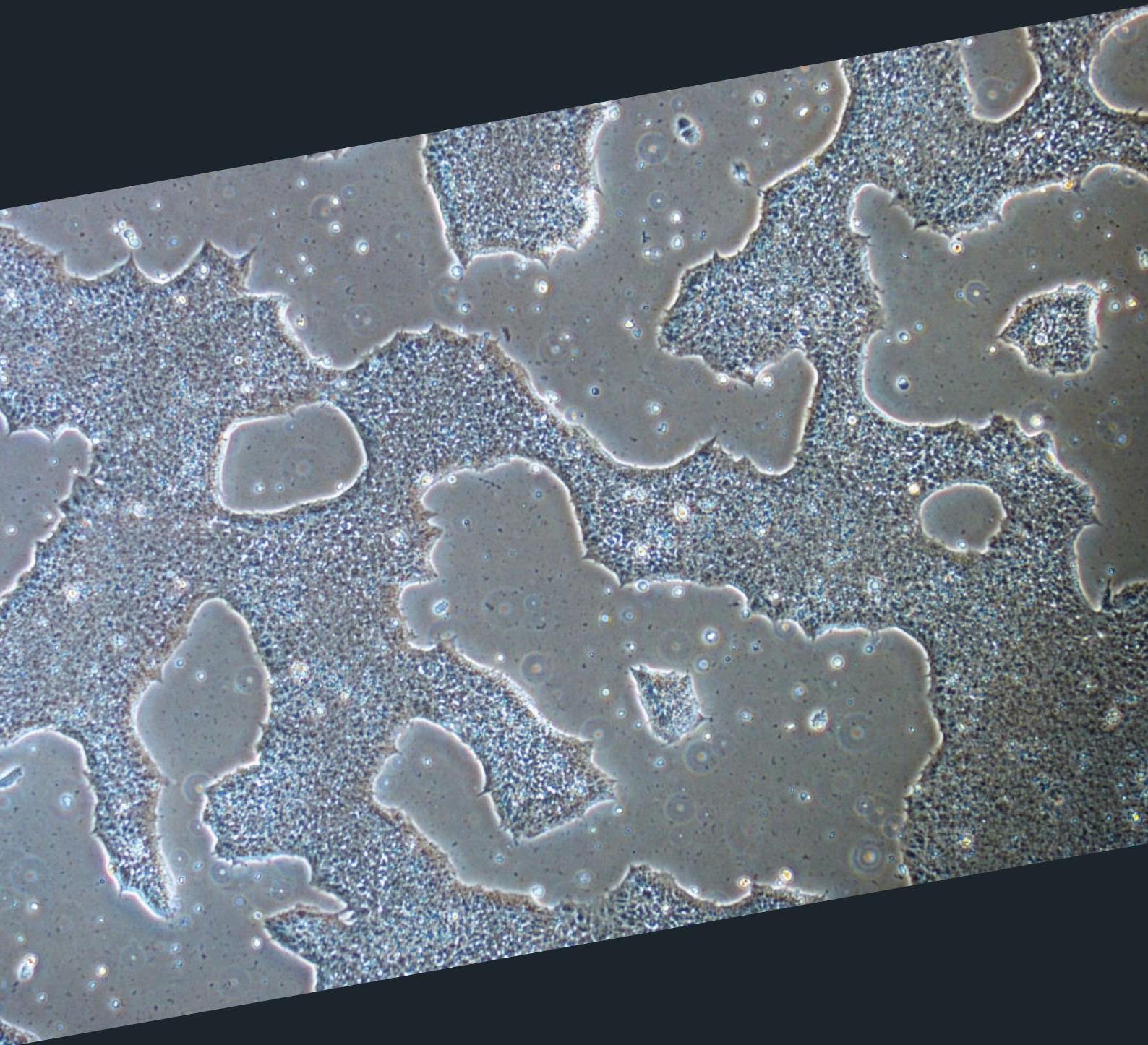


Image of cells by researcher Nadia Rajab, University of Melbourne



granted or with protection being sought. Of these, 2289 patent families have been granted, while 2961 families have patent protection being sought. The remaining 197 families are 'dead', having either lapsed or expired without being granted. The very low level of patent families in a 'dead' state may reflect the importance of patent protection in mammalian pluripotent stem cell technology development.

More details on patent status determination are shown in Appendix D: Patent Status Determination.

### Patent filing destinations

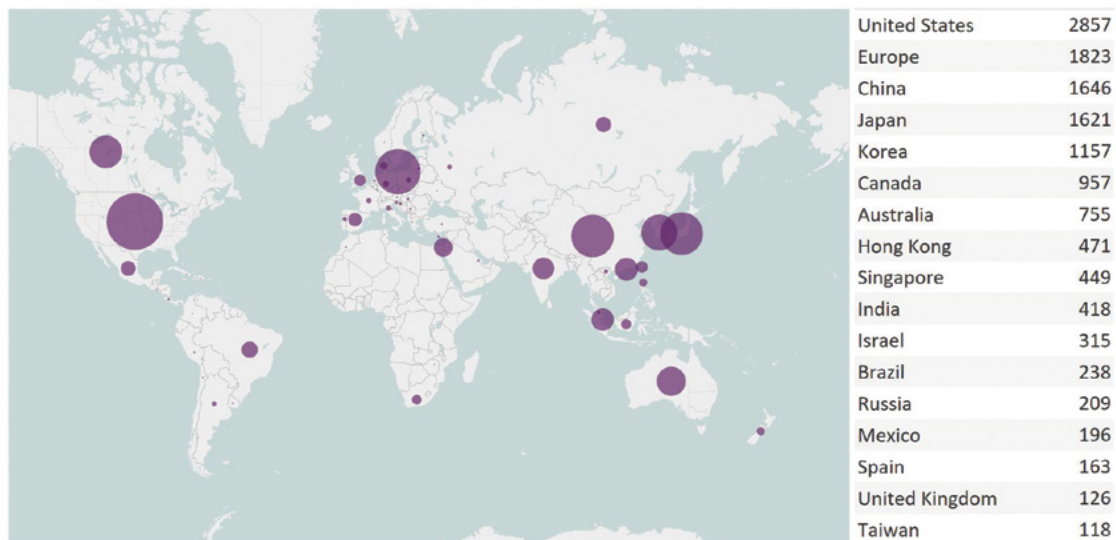
The target markets for inventions can be shown by the jurisdictions in which patent applications are filed. Applicants must file patents in each country in which they wish to have patent protection. The patent destination for inventions indicates where applicants choose to protect their invention. Reasons for protection include the country being a target for commercialisation or manufacture, or that

the country is important for further research. Figure 2 shows the volume of patent families filed by jurisdiction, with the top jurisdictions listed having at least 100 patent families filed.

Australia is the seventh largest target market for mammalian pluripotent stem cells technologies. The United States is the largest target market in this technology, with 2857 patent families filed here. This represents more than 50 per cent of the total patent families filed since 2008. Europe is the second largest target market with 1823 patent families filed in the European Patent Office (EPO). European patents are included in this analysis because they are enforceable in designated contracting states to the European Patent Convention at the date of filing of the application.<sup>4</sup> China is the third largest market, with 1646 patent families filed, closely followed by Japan in fourth place with 1621 patent families and Korea in fifth place with 1157 patent families.

Figure 2: Patent families relating to mammalian pluripotent stem cells by filing jurisdiction

Source: Derwent World Patent Index (accessed 29 October 2018)



(Note: Patent Corporation Treaty (PCT) applications have been excluded from this figure because they do not represent an enforceable right in any jurisdiction)

<sup>4</sup> EPO, [www.epo.org/law-practice/legal-texts/html/guidelines/e/a\\_iii\\_11.htm](http://www.epo.org/law-practice/legal-texts/html/guidelines/e/a_iii_11.htm)

## Applicant origin

Analysis of patent families by their origin indicates which countries have the most investment or interest in a specific area of research or innovation. Figure 3 shows countries in which the highest number of patent families originated. Country information is derived from applicant address data and applicant harmonisation, where possible.

Australia ranks fourteenth globally for patent families filed by Australian applicants, with 51 patent families filed by Australians since 2008. Although Australia is a large global target market, with 755 patent family applications filed in Australia, only five per cent of patents filed in Australia are filed by Australians. This indicates that either Australia has relatively little research in this area, or that Australian researchers are not seeking patent protection for their innovation in mammalian pluripotent stem cells.

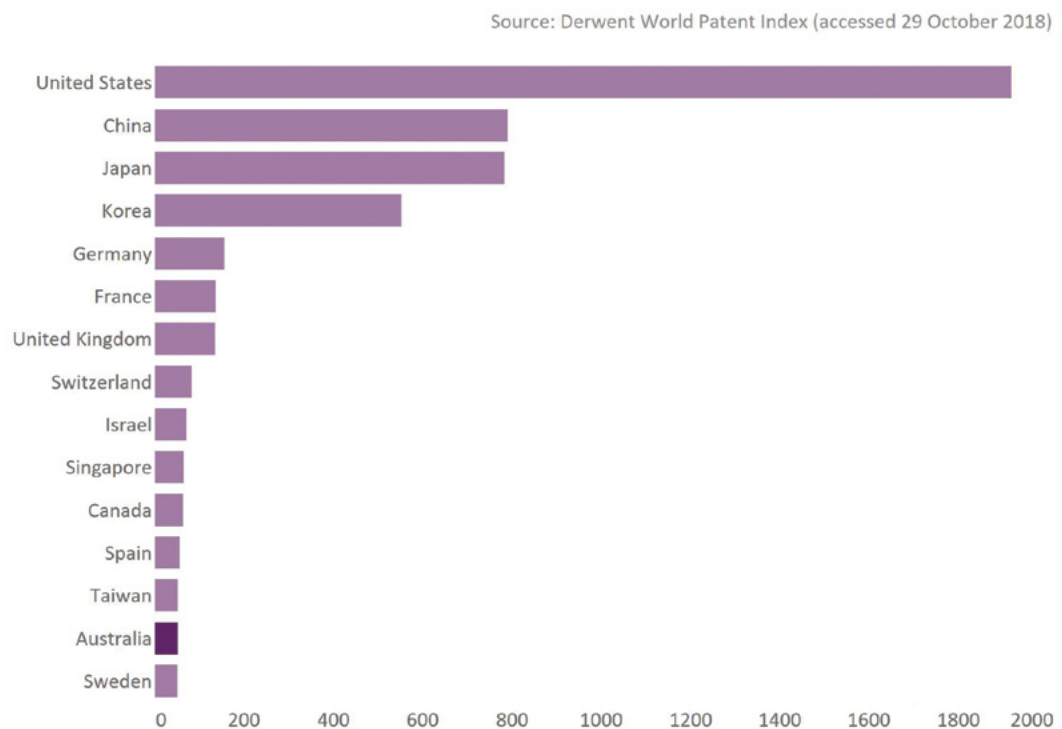
The United States is the most prominent country of origin in this technology. Applicants from the United States have filed 1919 patent families since 2008.

In second place is China with 790 patent families — less than half the number of patent families originating from the United States. The Chinese Academy of Sciences is the top patent filer in China in this technology, contributing to more than 10 per cent of patent families filed by Chinese applicants.

Japan is in third place, with 782 patent families filed since 2008. Kyoto University, who is the top patent filer globally, is responsible for 22 per cent of all patent families filed by Japanese applicants.

It is important to note that applicant origin country code data is missing for 781 patent families. Of these, 648 families have filings in a single country, and therefore the applicant is likely to originate from the filing country. While we have excluded such deduced country information from this analysis, we note that Japan, Korea, the United Kingdom and Israel each appear to be attributable to more than 50 patent families without applicant origin country code information. The inclusion of this data would not affect the position of the United States and Korea, but could elevate the position of Japan, United Kingdom and Israel.

Figure 3: Patent families relating to mammalian pluripotent stem cells by applicant origin



(Note: Patent Corporation Treaty (PCT) applications have been excluded from this figure because they do not represent an enforceable right in any jurisdiction)

### Top applicants

Entities file patents to protect their ideas and products. The number of patent families filed by an applicant in a particular technology can indicate their interest and market presence or a desire to build and maintain a market share. We identified the top applicants both globally, and in Australia, for inventions relating to mammalian pluripotent stem cells.

### Global applicants

Figure 4 shows the top 10 applicants of patent families relating to mammalian pluripotent stem cells. It is dominated by applicants from the research sector. The top 10 applicants together contributed 819 patent families, or about 15 per cent of total filings since 2008. Of these 819 patent families, 391 families (48 per cent) have been granted in at least one jurisdiction and 416 families (51 per cent) are seeking protection in at least one jurisdiction. This shows that these 807 patents, or 99 per cent of filings, are potentially of commercial value, and indicates a strong and current global interest in patent protection around mammalian pluripotent stem cells.

### Kyoto University

Kyoto University<sup>5</sup> is the most active applicant in mammalian pluripotent stem cells, with 172 patent families filed since 2008. From 2009–15 they have filed 152 patent families (21 patent families on average per year), with a top of 27 filings in 2013.

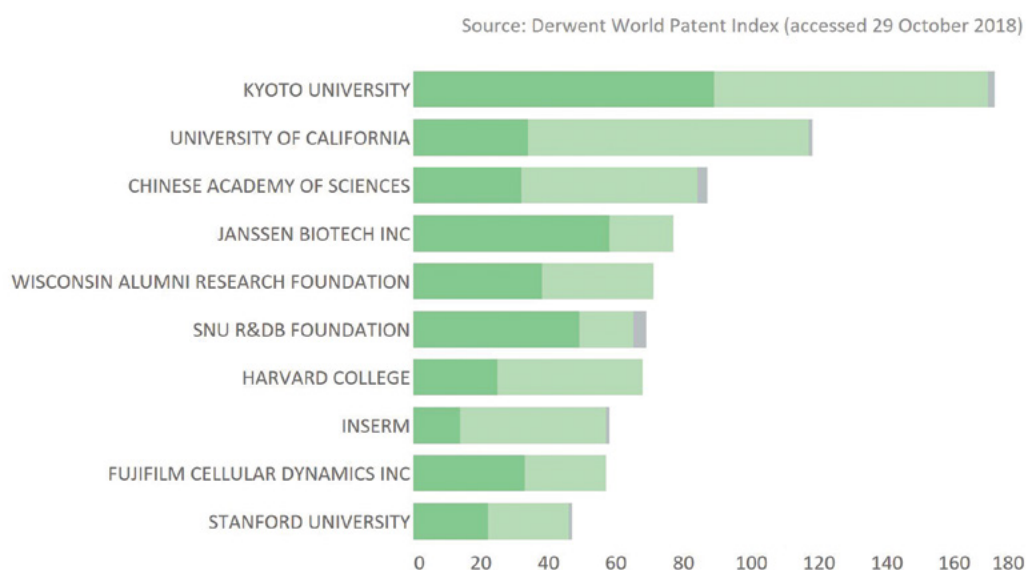
Inventions from this Japanese university are mainly in stem cell production (34 per cent), disease models (28 per cent) and differentiation (26 per cent). More details on Kyoto University are discussed in the stimulation and tissue engineering section of this report.

### University of California

The University of California is ranked second, with 118 patent families relating to mammalian pluripotent stem cells filed since 2008. Their patenting activity in the field shows an overall increasing trend from 2008–13, with a top of 20 patent families filed in 2013, after which the trend fluctuates over time.

The university's patent families have addressed stem cell production (24 per cent), disease models (24 per cent), stimulation and tissue engineering (21 per cent) and differentiation (21 per cent). More details on the University of California are discussed in the stimulation and tissue engineering section of this report.

Figure 4: Patent families relating to mammalian pluripotent stem cells by applicant



<sup>5</sup> Kyoto University, <https://www.kyoto-u.ac.jp/en/>

### Chinese Academy of Sciences

Founded in 1949, the Chinese Academy of Sciences is a flagship of China's drive to explore and harness technology and science.<sup>6</sup> They are now the world's largest research organisation, with around 60 000 staff across 104 research institutes, 12 branch academies, three universities and 11 supporting organisations in 23 provincial-level areas throughout the country.

Guangzhou Institutes of Biomedicine and Health,<sup>7</sup> of the Chinese Academy of Sciences, has pioneered Chinese stem cell research, and recently successfully created a system to culture stem cells automatically<sup>8</sup> as well as finding new methods to induce stem cells.<sup>9</sup>

The Chinese Academy of Sciences is ranked third in technology relating to mammalian pluripotent stem cells with 87 patent families filed since 2008, of which 19 families were filed in 2016. The academy's patent families concentrate on three technology categories: stem cell production (40 per cent), disease models (38 per cent) and differentiation (14 per cent).

### Janssen Biotech Inc

Janssen Biotech, Inc.,<sup>10</sup> formerly Centocor Biotech, Inc., is a biotechnology company, founded in 1979, with an initial goal of developing new diagnostic assays using monoclonal antibody technology. In 1999, Centocor – and therefore subsequently Janssen – became a wholly-owned subsidiary of Johnson & Johnson,<sup>11</sup> the worldwide manufacturer and marketer of healthcare products.

Janssen is developing treatments for patients in six therapeutic areas including cardiovascular and metabolism, immunology, infectious diseases and vaccines, neuroscience, oncology and pulmonary hypertension.<sup>12</sup> Janssen Belgium<sup>13</sup> participates in the Innovative Medicines Initiative (IMI) Stembanc,<sup>14</sup> a large-scale, five-year academic–industry partnership in stem cell research.

Janssen has filed 77 patent families relating to mammalian pluripotent stem cells since 2008, with a decreasing trend in patent families filed overtime from a peak of 17 patent families in 2008. Of these 77 patent families, 46 (58 per cent) relate to differentiation methods and 22 (28 per cent) relate to stem cell production.

### Wisconsin Alumni Research Foundation

Wisconsin Alumni Research Foundation (WARF)<sup>15</sup> partners with the University of Wisconsin-Madison to steward the cycle of research, discovery, commercialisation and investment.

Founded in 1925, WARF is a well-established and successful technology transfer office. WARF's portfolio of more than 1700 patents includes pluripotent stem cells, pharmaceuticals and medical devices.<sup>16</sup> WARF's pluripotent stem cell portfolio focuses on cell culture, differentiation and tools.<sup>17</sup>

We identified 71 patent families belonging to WARF that relate to mammalian pluripotent stem cells filed since 2008. In 2013, WARF filed 15 patent family applications, all predominantly related to disease models. Twenty-seven per cent of WARF patent families are related to differentiation, while 22 per cent relate to stem cell production.

<sup>6</sup> Chinese Academy of Sciences, [http://english.cas.cn/about\\_us/introduction/201501/t20150114\\_135284.shtml](http://english.cas.cn/about_us/introduction/201501/t20150114_135284.shtml)

<sup>7</sup> Guangzhou Institute of Biomedicine and Health, <http://english.gibh.cas.cn/>

<sup>8</sup> China Creates Medical Instrument to Culture Stem Cells Automatically, [http://english.cas.cn/newsroom/news/201805/t20180516\\_192542.shtml](http://english.cas.cn/newsroom/news/201805/t20180516_192542.shtml)

<sup>9</sup> Chinese Scientists Find New Method to Induce Stem Cells, [http://english.cas.cn/head/201804/t20180409\\_191525.shtml](http://english.cas.cn/head/201804/t20180409_191525.shtml)

<sup>10</sup> Janssen Biotech Inc., <https://www.janssen.com>

<sup>11</sup> Johnson & Johnson, <https://www.jnj.com/>

<sup>12</sup> About Janssen Biotech Inc., <https://www.janssen.com/about>

<sup>13</sup> Janssen Biotech Stem Cell Research, <https://www.janssen.com/belgium/exploring-new-frontiers-healthcare-stem-cell-research>

<sup>14</sup> Stembanc, <http://stembanc.org/>

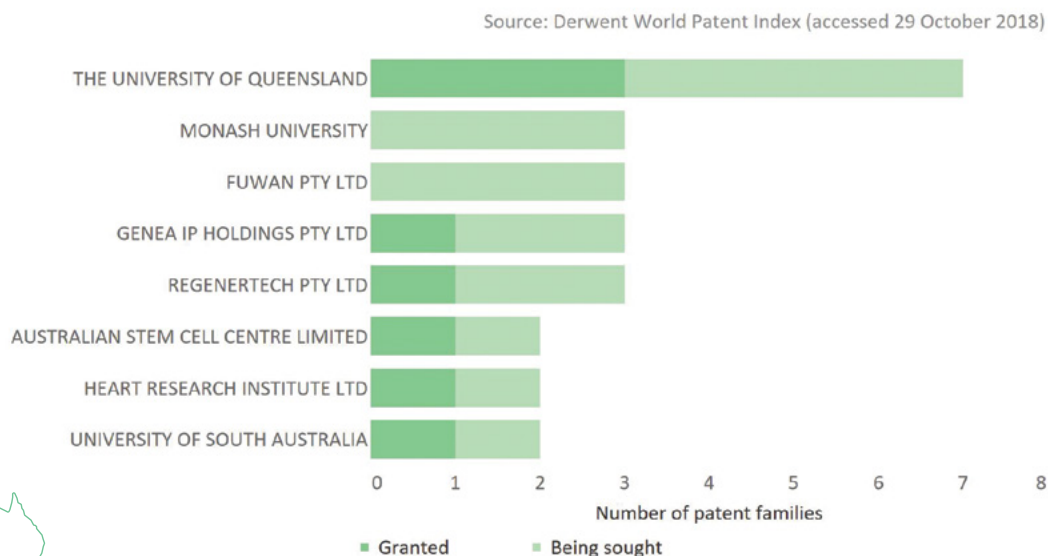
<sup>15</sup> Wisconsin Alumni Research Foundation, <https://www.warf.org>

<sup>16</sup> WARF's portfolio, <https://www.warf.org/technologies/inventions-patents-and-portfolios.cmsx>

<sup>17</sup> WARF's pluripotent stem cell portfolio, <https://www.warf.org/technologies/pluripotent-cells.cmsx>



Figure 5: Australian applicants filing patents relating to mammalian pluripotent stem cells



### Australian applicants

To better understand Australian patenting activity, we analysed data relating to Australian applicants in this technology. Figure 5 shows the top seven Australian applicants with two or more patent families.

The most prominent Australian patent applicant is the University of Queensland with seven patent families filed since 2008. Monash University, Fuwan Pty Ltd, Genea IP Holdings Pty Ltd and Regenertech Pty Ltd are in equal second position, each with three patent families, while Australian Stem Cell Centre Limited, Heart Research Institute Ltd and the University of South Australia are in equal third position, with two patent families.

### The University of Queensland

The University of Queensland (UQ) is one of the Group of Eight (Go8) of Australia’s eight leading research universities.<sup>18</sup> UQ has established eight research institutes with multidisciplinary focus in the areas of bioengineering and nanotechnology, molecular bioscience, social science, matter research, agriculture, brain research and mineral research. UQ is also a partner in the Translational Research Institute (TRI)<sup>19</sup> – a leading Australian initiative in biomedical research.

UniQuest,<sup>20</sup> established, in 1984 is UQ’s commercialisation entity, with a rich innovation portfolio including Australia’s first blockbuster vaccine Gardasil®, pioneer pain drug developer Spinifex Pharmaceuticals, the internationally acclaimed Triple P – Positive Parenting Program, and UQ’s superconductor technology, which is used in two-thirds of the world’s MRI machines.

UQ is active in stem cell research through its Centre in Stem Cell Ageing and Regenerative Engineering (StemCARE),<sup>21</sup> which aims to understand how declining stem cell function affects the ageing process, and to engineer translatable solutions for increasing health span and healthy ageing.

UQ is the top-ranked Australian applicant in innovation relating to mammalian pluripotent stem cells, with seven patent families, three of which have been granted in Australia, relating to stimulation and tissue engineering, differentiation and stem cell production.

### Monash University

Monash University hosts more than 100 research entities including ARC Centres of Excellence, Cooperative Research Centres, ARC Industrial Transformation Research Hubs and Centres, NHMC Centres of Research Excellence and Monash Institutes and Centres.

<sup>18</sup> The University of Queensland-Profile, <http://www.uq.edu.au/about/university-profile>

<sup>19</sup> Translational research institute, <https://www.tri.edu.au/about>

<sup>20</sup> UniQuest, <https://uniquest.com.au/>

<sup>21</sup> StemCARE, <https://aibn.uq.edu.au/uq-stemcare>



The university actively participates in stem cell research through the Development and Stem Cells program,<sup>22</sup> with 21 primary group leaders and their research teams. Their research interests range from genetic and molecular regulation of embryo and fetal development, kidney biology, through to stem cell biology and patterning, reproductive biology and the anatomy of the adult body.

In our analysis, Monash University ranked as the second highest Australian patent applicant in technology relating to the mammalian pluripotent stem cells, with three patent families filed since 2008, all relating to differentiation and disease models. Patent protection is being sought for all three patent families.

#### **Fuwan Pty Ltd**

Fuwan Pty Ltd was founded in 2012 and is recorded as 'deregistered' in Australian Securities & Investments Commission records.<sup>23</sup> Further details on the company are not available.

Fuwan Pty Ltd filed three patent families relating to mammalian pluripotent stem cells from 2012–14, all of which still have protection being sought.

#### **Genea IP Holdings Pty Ltd**

Genea Limited<sup>24</sup> provides assisted reproductive technology (ART) products and services in Australia, Thailand, New Zealand, and the United Kingdom. Formerly known as Sydney IVF Limited, Genea changed its name in November 2011.<sup>25</sup>

The company has three operational entities: Genea Fertility, Genea Biomedx, and Genea Biocells. Genea Fertility offers ART services through a network of clinics, as well as related consulting and education services through Genea Consult and the Centre of Excellence for Fertility. Genea Biomedx designs, manufactures, and sells IVF equipment, consumables, and media products.

Genea Biocells engages in discovery-stage drug development activities for treating neuromuscular disease.

We identified three patent families from Genea Limited relating to mammalian pluripotent stem cells. Of these three, one family has been granted in Australia.

#### **Regenertech Pty Ltd**

Regenertech Pty Ltd is an Australian private company registered in 2004 and was renamed to Enki Biotech Pty Ltd in 2010.<sup>26</sup>

This study found three patent families filed by Regenertech, one in 2008 and two in 2009, primarily relating to regenerative medicine. Of these three, one patent family has been granted in the United States.

<sup>22</sup> Development and Stem Cells, <https://www.monash.edu/discovery-institute/discovery-programs/development-and-stem-cells>

<sup>23</sup> ASIC registry search, [https://connectonline.asic.gov.au/RegistrySearch/faces/landing/panelSearch.jspx?searchText=160757504&searchType=OrgAndBusNm&\\_adf.ctrl-state=53keyip34\\_26](https://connectonline.asic.gov.au/RegistrySearch/faces/landing/panelSearch.jspx?searchText=160757504&searchType=OrgAndBusNm&_adf.ctrl-state=53keyip34_26)

<sup>24</sup> Genea Limited, <https://www.genea.com.au/>

<sup>25</sup> Company Overview of Genea Limited, <https://www.bloomberg.com/research/stocks/private/snapshot.asp?privcapId=53382243>

<sup>26</sup> ABN History-Regenertech, <http://www.abr.business.gov.au/AbnHistory/View?id=31101738318>



## Collaboration

Co-application on a patent gives a proxy indicator for collaboration. The ability to identify research partners collaborating through co-filing on patent applications is a key advantage of patent data.

### Global collaboration

Figure 6 shows the top 10 collaborating applicants in technology relating to mammalian pluripotent stem cells.

Kyoto University,<sup>5</sup> the most prominent patent filer in this technology, is also the top collaborator globally, and has collaborated with 48 other applicants on 61 patent families including universities, private companies and research organisations across the world. Kyoto University have collaborated most frequently with the Japanese National Institute of Advanced Industrial Science and Technology (six patent families). They also have collaborated with Osaka University<sup>27</sup> and the Japan Biological Informatics Consortium<sup>28</sup> on five patent families each, and with Keio University,<sup>29</sup> Astellas Pharma Inc.,<sup>30</sup> and Megakaryon Corporation<sup>31</sup> in four patent families each.

The French National Institute for Health and Medical Research (INSERM) is a public scientific and technological institute operating under the joint authority of the French Ministries of Health and Research.<sup>32</sup> INSERM is among the top 10 applicants in technology relating to mammalian pluripotent stem cells, and have filed 51 patent families in collaboration with 44 other applicants.

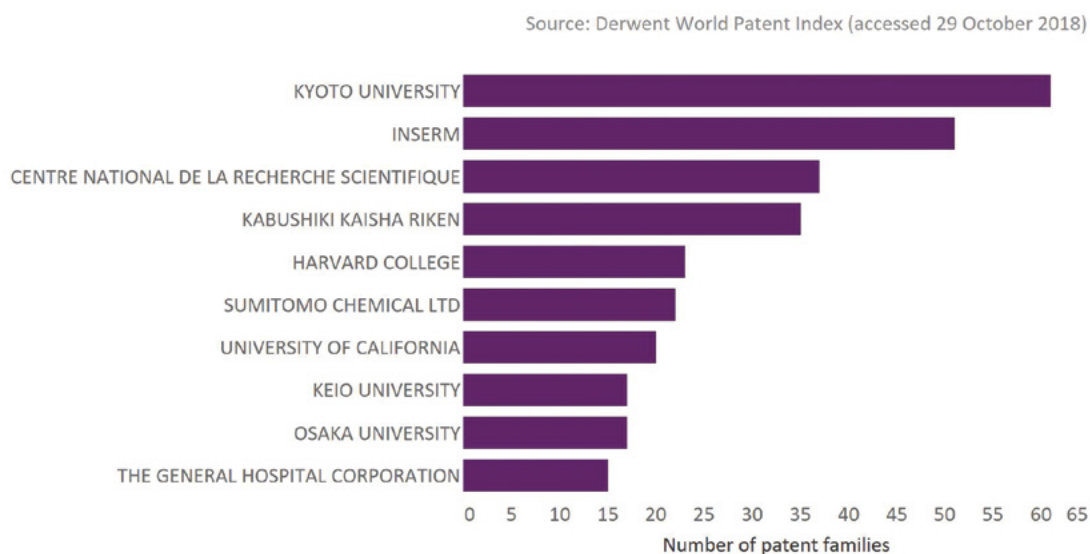
INSERM have collaborated with Centre National De La Recherche Scientifique (CNRS) on 22 patent families. CNRS<sup>33</sup> is the largest governmental research organisation in France and the largest fundamental science agency in Europe. They have collaborated with 40 other applicants on 37 patent families.

### Australian collaboration

There was limited collaboration on patent families by Australian applicants in this technology (Figure 7).

The University of Queensland, the top patent filer in Australia in mammalian pluripotent stem cells, has filed two patent families (WO2010069008 and WO2011091475) in collaboration with Griffith University and Australian Stem Cell Centre Limited, respectively.

Figure 6: Top global collaborators on patent families relating to mammalian pluripotent stem cells



<sup>27</sup> Osaka University, <https://www.osaka-u.ac.jp/en>

<sup>28</sup> Japan Biological Informatics Consortium, <http://www.jbic.or.jp/english/>

<sup>29</sup> Keio University, <https://www.keio.ac.jp/en/about/>

<sup>30</sup> Astellas Pharma Inc., <https://www.astellas.com/>

<sup>31</sup> Megakaryon Corporation, <http://www.megakaryon.com/en/>

<sup>32</sup> INSERM, <https://www.inserm.fr/en/about-inserm/inserm-glance>

<sup>33</sup> CNRS, Centre National De La Recherche Scientifique, <https://www.cnrs.fr/en>

Monash University has collaborated globally with Cell Mogrify Limited, Kabushiki Kaisha Riken and the University of Bristol in filing one patent family relating to transdifferentiation of a cell to a different cell type (WO2017106932A1).

The University of Melbourne also has filed one patent family in global collaboration with Auckland Uniservices Limited relating to stem cell production (WO2011096825A1).

Figure 7: Top Australian collaborators on patent families on mammalian pluripotent stem cells

Source: Derwent World Patent Index (accessed 29 October 2018)

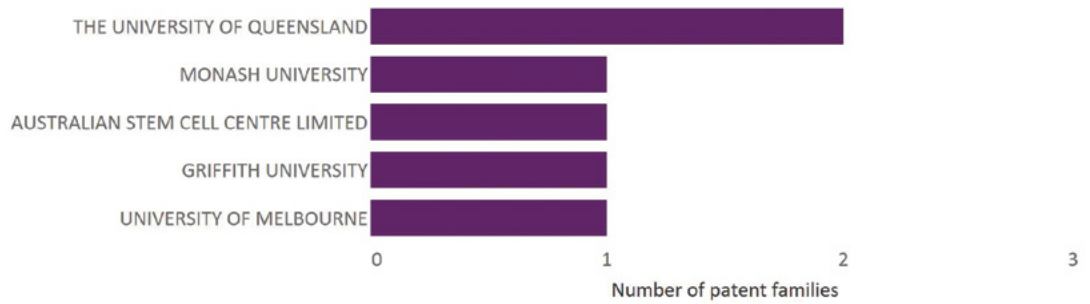
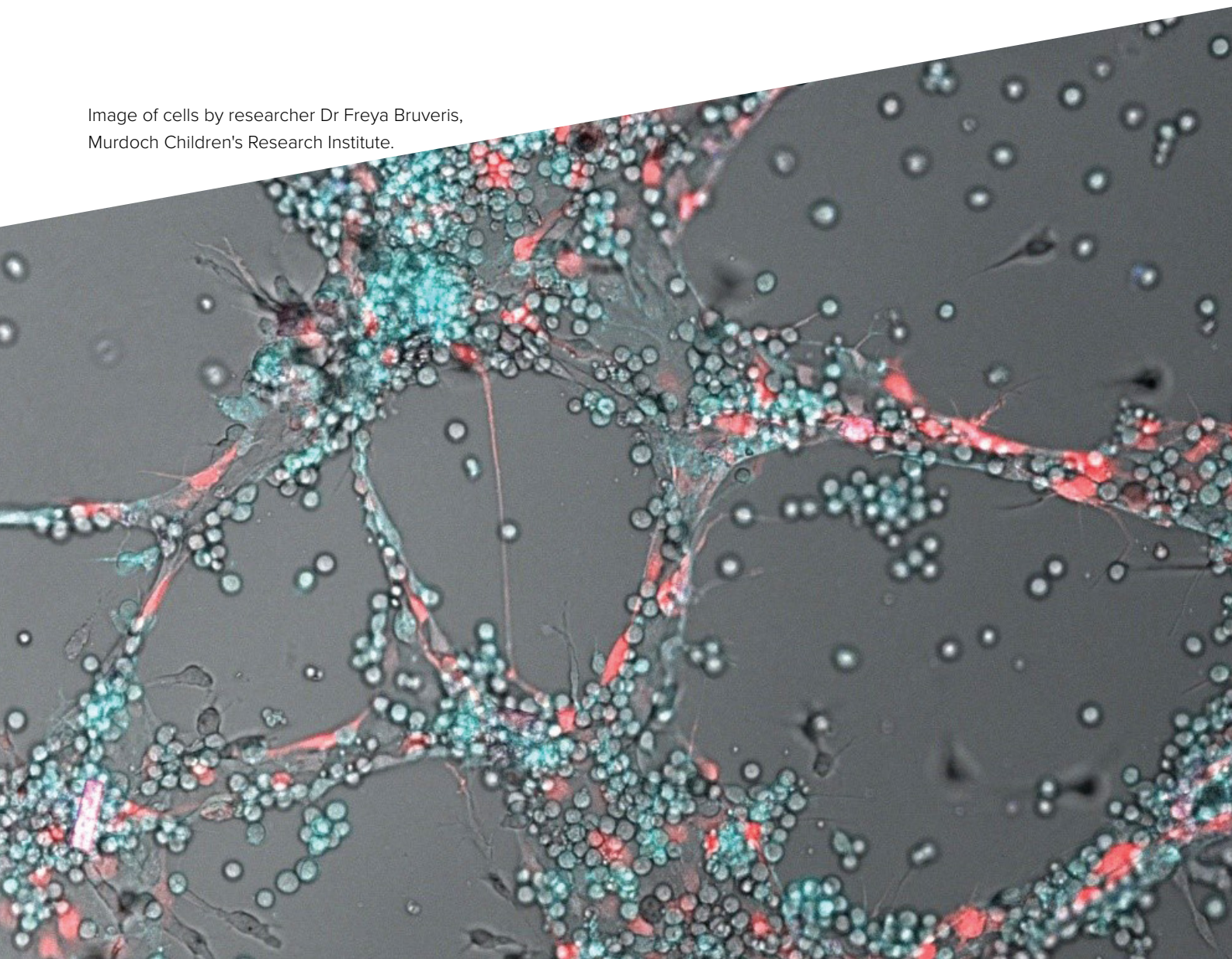


Image of cells by researcher Dr Freya Bruveris, Murdoch Children's Research Institute.



# TECHNOLOGY ANALYSIS

Technology analysis can be used to identify the level of activity in specific technology areas within a broad field. This analysis can help to understand areas of commercial interest, and can inform commercialisation strategies and research directions.

## Technology overview

We have divided the 5447 patent families identified in this study into five technology categories relating to mammalian pluripotent stem cells (Figure 8). In categorising these patent families overlap where families could be placed in multiple categories was noted. See Appendix C: Technology Analysis for more information about the technology classification.

- Stimulation and tissue engineering
- Differentiation
- Stem cell production
- Disease models
- Cryopreservation

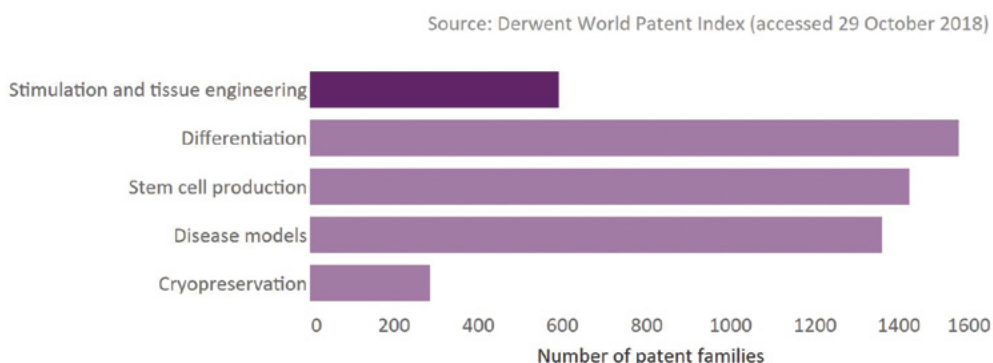
Of the above categories, stimulation and tissue engineering, differentiation and stem cell production

mainly fall within regenerative medicine. In contrast, disease models and cryopreservation are not usually associated with regenerative medicine. Regenerative medicine is the branch of medicine that seeks to develop new therapies to regrow, repair or replace damaged or diseased cells, tissues or organs.

We were unable to classify 244 patent families (4 per cent) into any of the five technology categories. Of these 244 families, 64 did not have English titles or abstracts in the DWPI database, and the remaining 180 patent families were identified as not fitting into any of these five technology categories.

**Stimulation and tissue engineering** includes applications with mammalian pluripotent stem cells that are specifically directed to the production of three-dimensional cellular structures or to external stimuli that can replace or repair damaged or diseased tissues with natural, synthetic, or semisynthetic tissue mimics. These mimics can either be fully functional or will grow into the

Figure 8: Technology analysis of patent families relating to mammalian pluripotent stem cells





required functionality. Tissue engineering includes inventions relating to self-aggregation/assembly and cellular scaffolds. We have identified 591 distinct patent families relating to stimulation and tissue engineering. This category will be further analysed and discussed in detail in the next section of this report.

**Differentiation**, with 1542 patent families, includes all applications directed to compositions and methods for general differentiation or for differentiation into specific cell types. This category also includes applications directed to the use of differentiated cells in cell therapy, such as by the direct administration of stem cells or differentiated stem cells for therapeutic purposes including repair of injured or diseased tissues or organs.

The top three applicants in the category relating to differentiation are Janssen Biotech Inc. (46 patent families: 35 granted and 11 being sought), Kyoto University (45 patent families: 21 granted and 24 being sought) and University of California (25 patent families: 8 granted and 17 being sought).

An example of a patent application in the differentiation category is WO2010051213A1, filed by Janssen Biotech Inc. on methods to differentiate pluripotent stem cells into cells expressing markers characteristic of the pancreatic endocrine lineage. The methods involve treating the cells with medium comprising a TGF- $\beta$  receptor agonist selected from activin A, activin B, activin C, peptide variants of activin A, GDF-8, GDF-11 and GDF-15.

Patent application WO2013151186A1, filed by Kyoto University, outlines a method for inducing differentiation of erythropoietin-producing cells from human pluripotent stem cells in which the cells are cultured in medium containing activin and a GSK-3 $\beta$  inhibitor, and then in a medium containing an insulin-like growth factor (IGF) family gene product such as IGF-1.

The University of California filed patent application WO2013184809A1, relating to a culture media and method for the differentiation of pluripotent stem cells into retinal pigmented epithelium cells. The method comprises culturing pluripotent cells in a series of basal mediums supplemented with combinations of insulin-like growth factor 1 (IGF-1), Dickkopf-related protein (DKK1), noggin, basic fibroblast growth factor (BFGF), Activin A and SU5402 (an FGF signalling inhibitor).

**Stem cell production**, with 1425 patent families, includes patents directed to isolation or separation methods, cellular reprogramming or dedifferentiation methods and culture methods relating to pluripotent stem cells.

Kyoto University (55 patent families: 29 granted, 28 being sought and 1 dead), the Chinese Academy of Sciences (35 patent families: 14 granted, 20 being sought and 1 dead) and the University of California (28 patent families: 8 granted and 20 being sought) are the top three applicants in technology relating to stem cell production.

Kyoto University filed patent application WO2009133971A1, describing a method of producing an iPS cell by introducing one or more non-viral expression vectors encoding the reprogramming factors Sox-2, Oct-4, Nanog and Lin28 into somatic cells.

Patent application WO2013056535A1, filed by the Guangzhou Institute of Biomedical and Health of the Chinese Academy of Sciences outlines a method for increasing the efficiency of inducing pluripotent stem cells in which genes encoding the histone-modifying transcription factors, Jhdm1b and Jhdm1a, are transferred into adult mammalian cells before culturing in medium containing vitamin C and combinations of the reprogramming factors Oct4, Klf4, Sox2 and c-Myc.

Another example is patent application WO2011143400A2, filed by the University of California, who have developed compositions and methods for inducing human pluripotent stem cells in which cells are treated with a reprogramming culture medium that also contains fibromodulin, a small leucine rich proteoglycan.

**Disease models**, with 1360 patent families, relates to the production of genetically modified organisms or specific cell types as models of disease states. Kyoto University (49 patent families: 27 granted, 21 being sought and 1 dead) is the most prominent patent filer in this category. The Chinese Academy of Sciences (33 patent families: 10 granted, 22 being sought and 1 dead) ranked second, while The University of California (28 patent families: 7 granted and 21 being sought) and the WARF (28 patent families: 13 granted and 15 being sought) ranked equal third.



**Cryopreservation**, with 285 patent families, includes families relating to compositions and methods for the cryopreservation of pluripotent stem cells and/or cells derived from these stem cells. Guangzhou Saliat Stemcell Science and Technology (8 patent families, all being sought), Anthrogenesis Corporation (4 patent families, 1 granted, 3 being sought) and Beijing Regeneration Biotechnology Inst Co. Ltd. (4 patent families, all being sought) are the top three applicants in this technology.



Matt Rutar looking at slide  
Photographer: Gavan Mitchell from The University of Melbourne



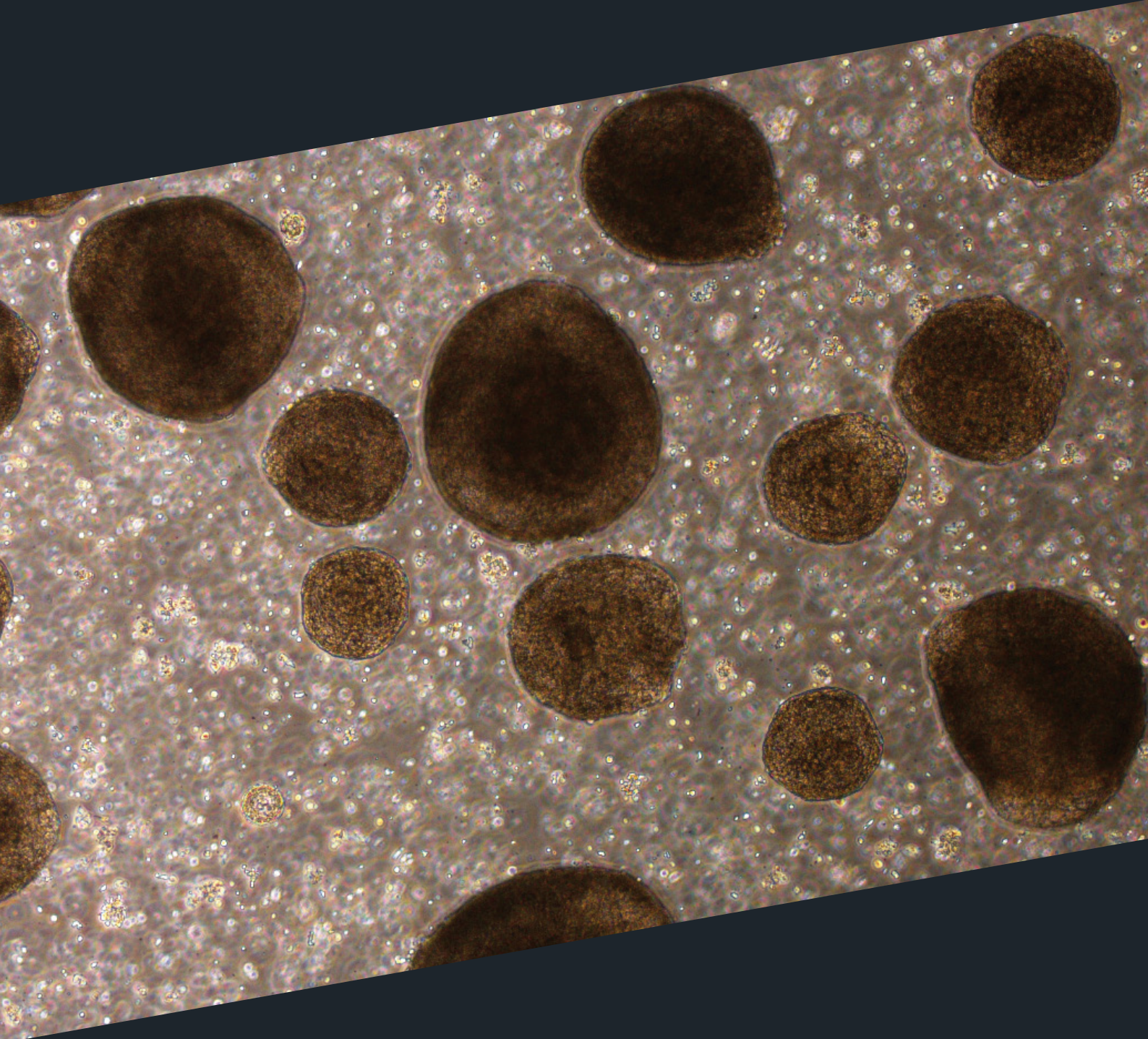


Image of cells by researcher Nadia Rajab, University of Melbourne

## STIMULATION AND TISSUE ENGINEERING

This section focuses on the 591 unique patent families that relate to stimulation and tissue engineering with mammalian pluripotent stem cells. This area of research is of particular interest to the Centre for Stem Cell Systems of the University of Melbourne.

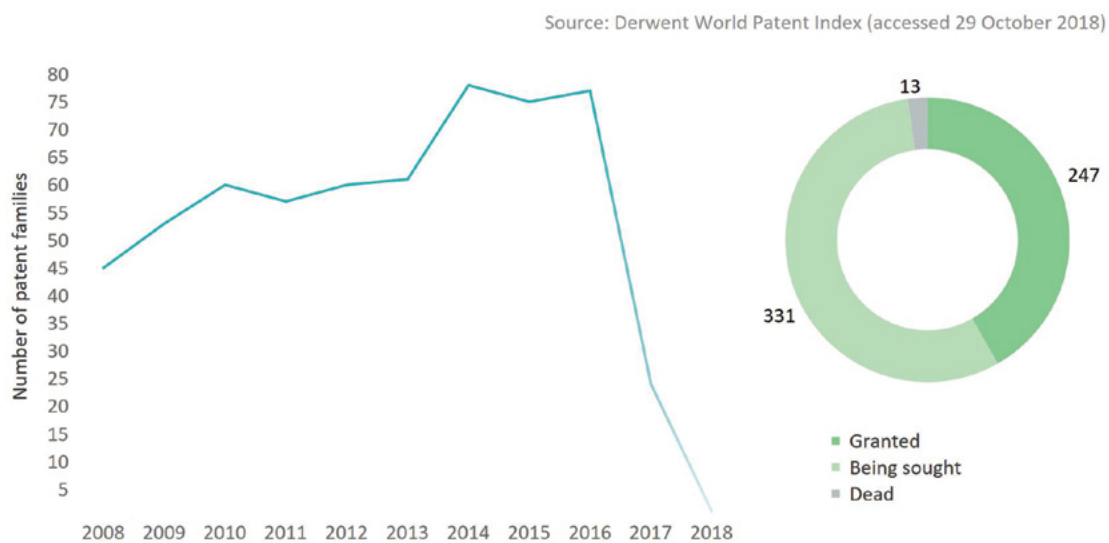
### Timeline

The number of patent families relating to stimulation and tissue engineering of mammalian pluripotent stem cells, by status and earliest priority year

is shown in Figure 9. Patenting activity in this technology shows an increasing trend from 45 patent families in 2008 up to a peak of 78 patent families in 2014 after which filing numbers fluctuate slightly.

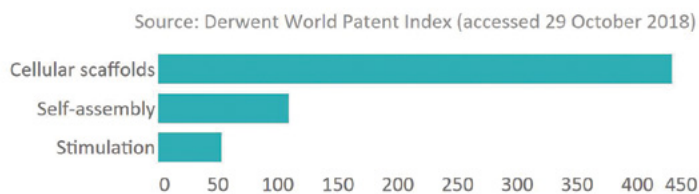
Of the 591 patent families filed since 2008, 247 have been granted in at least one jurisdiction, while there are 331 with protection being sought. The low number of dead patent families (2 per cent) indicates the importance of patent protection in this technology.

Figure 9: Patent families relating to stimulation and tissue engineering of mammalian pluripotent stem cells by status and earliest priority year



(Note: data for 2017–18 is incomplete due to a lag in patent publication: the dip in this timeline reflects incomplete data rather than a declining trend in applications)

Figure 10: Technology analysis of patent families relating to stimulation and tissue engineering



### Subcategories of stimulation and tissue engineering

We further divided the 591 patent families relating to stimulation and tissue engineering into three subcategories: stimulation, self-assembly and cellular scaffolds, using keywords in titles and abstracts of the individual patent applications (see Appendix C: Technology Analysis for further information). Figure 10 shows the number of patent families in each subcategory.

**Stimulation** includes stimulation using external stimuli such as electric/electromagnetic, light, magnetic or shear stress. We have identified 53 patent families filed since 2008 relating to stimulation. Of these patent families, 25 have been granted and 26 have protection being sought. The low number of dead patent families (4 per cent) indicates the interest in patent protection in this area. The relatively low patenting activity in this category indicates the potential for further innovation.

Stanford University filed patent application WO2009155369A1, describing an optogenetic technology for selectively controlling the growth and development of pluripotent stem cells in a biological environment. The stem cells are genetically modified to express a microbial opsin that enables light to be used to selectively influence these cells independently from the other types of cells in the immediate environment.

Patent application WO2012006320A1, filed by Harvard College introduces photosensitive, cardiac rhythm modulation structures comprising genetically-engineered tissue containing a population of pacing cells expressing a photosensitive membrane transport mechanism that is responsive to light of particular wavelengths.

Patent application WO2012053718A9, filed by Dongguk University outlines a method for differentiation of mesenchymal stem cells into neural cells after exposure to an electromagnetic field.

**Self-assembly** applications relate to self-aggregation/assembly or scaffold-mediated aggregation/assembly of cells. This analysis found 109 patent families relating to this subcategory, with 47 granted in at least one jurisdiction and 58 with protection being sought.

Patent application WO2016022930A1, filed by the University of California, describes a method of inducing self-assembly of mammalian cells, including pluripotent stem cells, into three-dimensional micro-tissues in which cells are seeded into patterned micro-wells that facilitate cell alignment and self-assembly.

Stanford University's patent application WO2018191656A1 outlines a three-dimensional suspension culture system in which human pluripotent stem cells are differentiated in vitro into oligodendro-spheroids comprising oligodendrocytes.

A patent application that includes both self-assembly and scaffolds is WO2017070506A1, filed by Indiana University Research and Technology Corporation. This patent outlines a method for producing skin organoids from pluripotent stem cells. The method involves culturing human pluripotent stem cell aggregates in a culture medium with Bone Morphogenetic Protein 4 (BMP4) and an inhibitor of Transforming Growth Factor Beta signalling to produce non-neural epithelium within the aggregates. The aggregates are then embedded in a porous substrate that includes extracellular matrix components, and are cultured under conditions that promote self-assembly of cells within the embedded



aggregates into a three-dimensional, multilayered composition with an epidermal layer, a dermal layer, and cells capable of forming a functional hair follicle.

**Cellular scaffolds** includes patent applications that describe the use of all synthetic polymeric materials (including hydrogels and gels) and all natural scaffolds produced from decellularised extracellular matrix, matrix proteins or self-assembling peptides. This analysis found 429 patent families relating to this subcategory, with 175 of these granted in at least one jurisdiction and 247 with protection being sought.

Examples include patent application US20130251687A1, by the University of California, describing the use of decellularised extracellular matrix derived from cardiac or skeletal muscle tissue, and culturing cells, such as pluripotent stem cells, on the matrix scaffold.

Kyoto University and Gunze Ltd have a collaborative patent application US20170319747A1, that describes a cell culture substrate with a biodegradable polymer nanofiber that can be seeded with cells and used for three-dimensional cell culture. The cell loaded substrate can be directly used as an agent for a cell transplantation therapy.

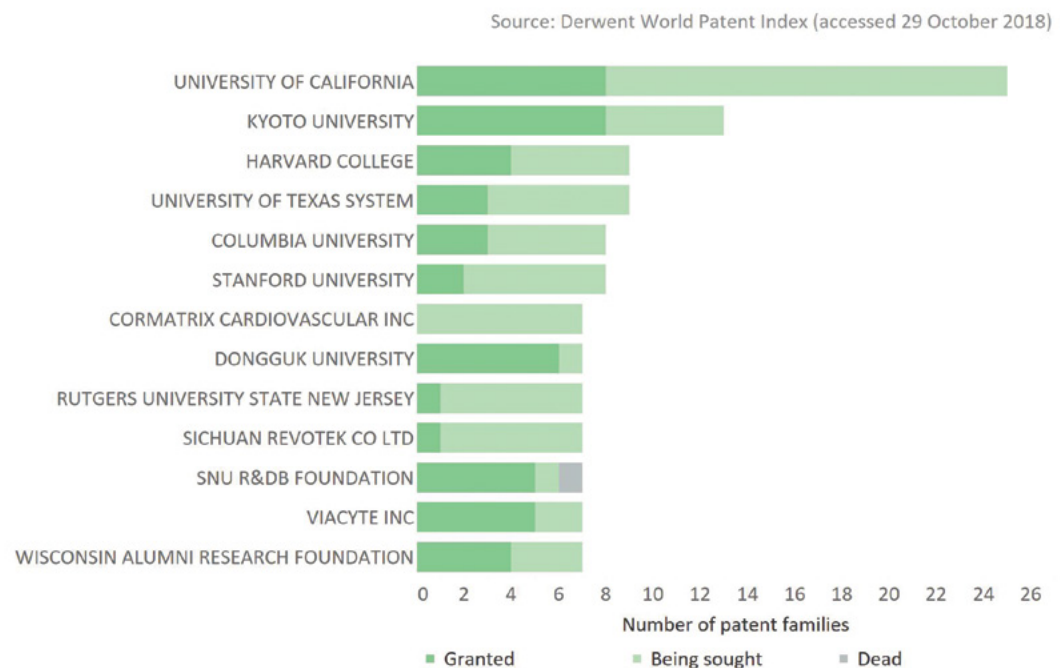
Harvard College's patent application US20140079752A1 describes compositions and methods to form pores in situ within hydrogels following hydrogel injection. Porosity influences recruitment and egress of cells from the composition. Stem cells may be included within the hydrogel compositions and can be released during hydrogel degradation following administration.



Matt Rutar putting away slide  
Photographer: Gavan Mitchell from The University of Melbourne



Figure 11: Patent families relating to stimulation and tissue engineering by applicant



### Top applicants

Figure 11 shows the top applicants with seven or more inventions relating to stimulation and tissue engineering with mammalian pluripotent stem cells. The top applicants are predominantly from the research sector.

The top 13 applicants contributed 121 (20 per cent) patent families, out of the total of 591 unique patent families filed since 2008.

Out of 121 patent families, 120 are either granted in at least one jurisdiction or in an active state seeking protection in at least one jurisdiction. This indicates that all of these patents are potentially of commercial value to these applicants.

#### The University of California

The University of California is the top patent filer in this technology with 25 patent families since 2008. Of these 25 families, 8 have been granted in at least one jurisdiction and 17 are in an active state with protection being sought.

The Sue & Bill Gross Stem Cell Research Centre of the University of California, Irvine<sup>34</sup> is pioneering research into stem cell therapies for Huntington's, Alzheimer's, Parkinson's, spinal cord injury, traumatic

brain injury, cancer, diabetes, retinitis pigmentosa, multiple sclerosis, and other diseases and conditions. It is a world leader in research, having developed the first federally-approved human trial of an ES cell treatment.<sup>35</sup>

#### Kyoto University

Kyoto University's Centre for iPS Cell Research and Application (CiRA)<sup>36</sup> is a world-leading iPS cell research institute. The centre was founded in 2008 as a part of the Institute for integrated Cell-Material Science (iCeMS). CiRA is organised into five departments focusing on reprogramming, cell growth and differentiation, clinical applications, fundamental cell technology, and ethics. CiRA has been working towards establishing basic iPS cell technologies, acquiring patents, building an iPS cell bank, conducting preclinical and clinical research, and supporting drug screening and development.

We have identified 13 patent families filed by Kyoto University that relate to stimulation and tissue engineering with mammalian pluripotent stem cells; 8 of these have been granted in at least one jurisdiction and the remaining 5 are in an active state with protection being sought.

<sup>34</sup> Stem Cell Research Center of University of California Irvine, <http://stemcell.uci.edu/about/>

<sup>35</sup> UC Irvine Stem Cell Research Center, <https://ucistemcellresearchcenter.wordpress.com/about/>

<sup>36</sup> CiRA, Kyoto University, <http://www.cira.kyoto-u.ac.jp/e/about/>

### **Harvard College**

Harvard College is the undergraduate liberal arts and sciences college of Harvard University.<sup>37</sup>

Harvard Stem Cell Institute (HSCI)<sup>38</sup> is a Harvard-affiliated research facility established in 2004 to pursue the promise of stem cell science and regenerative medicine. Some of the breakthroughs by HSCI scientists include developing healthy insulin-producing cells that can be given to diabetes patients, discovering a new type of lung cell responsible for cystic fibrosis, discovering how to collect 'overachieving' blood stem cells rapidly, which is an important step in improving bone marrow transplants, converting stem cells to specific kinds of tissue (such as heart muscle or nerves), and developing drugs to stimulate repair by tissue-resident stem cells (such as in the ear or in skeletal muscle).<sup>39</sup>

This analysis found 9 patent families filed by Harvard College relating to stimulation and tissue engineering with mammalian pluripotent stem cells, of which 4 have been granted in at least one jurisdiction and the remaining 5 are in an active state with protection being sought.

### **University of Texas System**

The University of Texas System is a government entity of the state of Texas that oversees 14 educational institutions including 8 universities and 6 health institutions.<sup>40</sup>

The University of Texas Health Science Centre at Houston hosts The Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases (IMM), which focuses on studying and preventing diseases at the genetic, cellular and molecular levels using DNA and protein technologies and animal models.<sup>41</sup> IMM studies the fundamental properties of stem cells, to translate their unique biological properties into cellular therapies for graft engineering and tissue regeneration for currently intractable disorders through its Center for Stem Cell & Regenerative Medicine.<sup>42</sup>

We have identified 9 patent families assigned to The University of Texas System relating to stimulation and tissue engineering with mammalian pluripotent

stem cells, of which 3 have been granted in at least one jurisdiction and the remaining 6 are in an active state with protection being sought.

### **Columbia University**

Columbia University hosts the Audubon Biotechnology and Research Park, positioned at the forefront of medical research. As New York City's only university-related research park, it contributes to economic growth through the creation of private-sector research collaborations and the generation of new biomedical related business.

Colombia Stem Cell Initiative is a stem cell research facility that brings together scientists from the many schools and affiliate hospitals of Columbia University to advance scientific discovery in stem cell biology and tissue regeneration and develop stem cell-based treatments for patients.<sup>43</sup>

This analysis found 8 patent families filed by Columbia University relating to stimulation and tissue engineering with mammalian pluripotent stem cells, of which 3 have been granted in at least one jurisdiction and the remaining 5 are in an active state with protection being sought.

### **Stanford University**

Stanford University has been a leader in stem cell research for the past quarter-century. The establishment of the Institute for Stem Cell Biology and Regenerative Medicine in 2002 has set the foundation for the creation of a new field of science: regenerative medicine. The institute studies how stem cells are created, the mechanisms by which they are regulated and how they devolve into specialised cells.<sup>44</sup> The four major research areas include mature tissue or organ stem cells, human ES and iPS cells, new stem cell lines, and cancer stem cells.

We have identified 8 patent families filed by Stanford University relating to stimulation and tissue engineering with mammalian pluripotent stem cells, with 2 of these granted in at least one jurisdiction and the remaining 6 in an active state with protection being sought.

<sup>37</sup> Harvard University, <https://www.harvard.edu/>

<sup>38</sup> Harvard Stem Cell Institute, <https://hsci.harvard.edu/about-us>

<sup>39</sup> HSCI-Who We Are, <https://hsci.harvard.edu/accomplishments-and-goals>

<sup>40</sup> University of Texas Systems-Institutions, <https://www.utsystem.edu/institutions>

<sup>41</sup> IMM, <https://www.uth.edu/imm/index.htm>

<sup>42</sup> IMM- Center for Stem Cell & Regenerative Medicine, <https://www.uth.edu/imm/centers/stem-cell-research.htm>

<sup>43</sup> CSCI, <https://www.stemcell.columbia.edu/about-us>

<sup>44</sup> Institute for Stem Cell Biology and Regenerative Medicine, <http://med.stanford.edu/stemcell/about.html>

### **Applicant origin and patent filing destinations**

The top countries of origin for patent families relating to stimulation and tissue engineering is similar to that of the overall technology of mammalian pluripotent stem cells. Australia ranks thirteenth, and the United States is top with 284 patent families. The top patent filing destinations for

stimulation and tissue engineering mirror that of the overall technology of mammalian pluripotent stem cells. Australian is seventh largest target market and the United States is the largest



## CONCLUSION

This report set out to explore the patent landscape of innovation relating to mammalian pluripotent stem cells.

It found a total of 5447 patent families have been filed, since 2008, in the field of mammalian pluripotent stem cells. This field has seen continuous growth, with the number of patent families filed increasing from 485 in 2008 to 680 in 2016.

The technology is dominated by applicants from the United States, who account for 35 per cent of the total patent families filed. China and Japan rank second and third, each representing 14 per cent of patent families filed. The most popular patent filing destination for mammalian pluripotent stem cell patents is the United States with 52 per cent of patent families filed, followed by Europe with 34 per cent.

Australia is the seventh largest target market while Australian applicants rank fourteenth for patent families by country of origin relating to mammalian pluripotent stem cells.

Patent families in this technology are predominately directed at differentiation (28 per cent) and stem cell production (26 per cent).

Stimulation and tissue engineering, an area of interest to the Centre for Stem Cell Systems, encompasses 11 per cent of the total patent families relating to mammalian pluripotent stem cells. The high number of patent families granted or with protection being sought (98 per cent) for stimulation and tissue engineering is indicative of the importance of patent protection in this technology.

This analysis shows that innovation in mammalian pluripotent stem cells is dominated by universities and research institutes and has a healthy level of collaboration. This indicates the technology is in the early stages of development. It is a growing field with huge opportunities for translating research into applications as the technology matures.

## APPENDIX A: DEFINITIONS

### Patents, applications and publications

A patent is a right that is granted for any device, substance, method or process that is new, inventive and useful. Australian patent rights are legally enforceable and give the owner, or patentee, exclusive rights to commercially exploit the invention in Australia for a period of up to 20 years. In this report, an application refers to a single patent filing. A patent application is usually published within 18 months of its earliest filing date (also known as the priority date). We consider that the priority date is most relevant for our analysis as it is the closest date to that when the invention occurred.

There are two major routes for filing a patent application: international route and direct filing. The international route involves filing a PCT application, which establishes a filing date in all 152 contracting states.<sup>45</sup> Subsequent prosecution at national patent offices, referred to as national-phase entry, is made at the discretion of the applicant. A patent can only be enforced once it has been granted and a PCT application must enter the national-phase to proceed towards grant. Alternatively, applications can be filed directly in the countries of interest.

### Patent families

Applications filed in different jurisdictions but claiming the same priority are known as patent families. Patent families enable us to analyse inventive activity regardless of the number of

countries in which protection is sought. Patent families are commonly used in analytics as they generally represent a single invention. In this analysis, we determined patent families based on DWPI database definition. In a DWPI patent family each member shares exact priorities with each and every other family member.<sup>46</sup> The DWPI database also contains INPADOC patent families, which give a unique family ID to patents that share a common priority document.<sup>47</sup> For metrics, the number of patent families is typically used. There are some exceptions where individual applications are reported on, as each application represents a legal right in an individual country. When analysing the number of applications or families per applicant, relating commercial entities have been grouped under a single, harmonised applicant name. When individual publication numbers are quoted, we have chosen a representative publication from the respective patent family.

### Classification

Patents are classified by technology into the hierarchical IPC system. A further classification system, as referenced in this report, is the CPC. The CPC began in 2013 and is a bilateral system developed by the EPO and the US Patent and Trademark Office, providing significantly more depth to the hierarchy of the IPC.<sup>48</sup> For more information on the coverage of the CPC, see the CPC Annual Report 2016.<sup>49</sup>

<sup>45</sup> WIPO, [www.wipo.int/pct/en/pct\\_contracting\\_states.html](http://www.wipo.int/pct/en/pct_contracting_states.html)

<sup>46</sup> Derwent Innovation: DWPI and INPADOC Family Criteria, [https://support.clarivate.com/Patents/s/article/Derwent-Innovation-DWPI-and-INPADOC-Family-Criteria?language=en\\_US](https://support.clarivate.com/Patents/s/article/Derwent-Innovation-DWPI-and-INPADOC-Family-Criteria?language=en_US)

<sup>47</sup> Martinez, 'Insight into Different Type of Patent Families', OECD Science, Technology and Industry Working Papers, No. 2010/2, OECD Publishing, Paris; see section 3.2, 'Extended families'.

<sup>48</sup> Cooperative Patent Classification, [www.cooperativepatentclassification.org/](http://www.cooperativepatentclassification.org/)

<sup>49</sup> CPC Cooperative Patent Classification Annual Report 2016, [www.cooperativepatentclassification.org/publications/AnnualReports/CPCAnnualReport2016.pdf](http://www.cooperativepatentclassification.org/publications/AnnualReports/CPCAnnualReport2016.pdf)



## APPENDIX B: SEARCH STRATEGY

Searching patent information to identify relevant records for analysis requires a stepped approach to identify broad categories of relevance, and then specific records within them that meet the technology brief.

The following outlines the detail of the search and analysis process conducted.

### Data extraction and analysis

We used four phases of data extraction and analysis.

- Phase 1: Development of a search strategy (below).
- Phase 2: Data mining using the DWPI database via Derwent Innovation. The unique DWPI family

members relating to mammalian pluripotent stem cells were identified and used as the basis of the analysis. In cases where the DWPI family id was not available the INPADOC family id was used.

- Phase 3: Data cleaning, to remove data duplications and consolidate applicant names.
- Phase 4: Data analysis using Tableau 2018.2 for calculations and visual presentation of patent metrics.

### Search strategy

The search was limited to patent applications that had an earliest filing date on or after 2008, and used CPC/IPC symbols and keywords.

Search Area	Search Query
(Pluripotent stem cells, reprogramming, ES cells) AND Mammalian cells	{(CTB=((nuclear OR cell* OR pluripoten* or ipsc? OR ips?) NEAR6 (reprogram* OR re-program*)) OR ((reprogram* OR re-program*) NEAR4 (factor? OR cocktail?)) OR (epigenetic* NEAR6 (reprogram* OR re-program*)) OR dedifferentiat* OR de-differentiat* OR transdifferentiat* OR trans-differentiat* OR ((lineage OR direct*) NEAR6 (reprogram* OR re-program*)) OR (direct* NEAR6 differentia*) OR redifferentiat* OR re-differentiat* OR (pluripotent ADJ ((stem ADJ cell?) OR progenitor?)) OR ((hiPS OR miPS OR riPS) ADJ cell?) OR (induced ADJ4 (stem OR progenitor) ADJ cell?) OR (hiSC? OR miSC? OR riSC? OR hipSC? OR mipSC? OR ripSC?)) AND (PRY>=(2008)); OR (AIC=(C12N2506* OR C12N00050696 OR C12N00050607)) AND (PRY>=(2008)) OR (CTB=((embryonic OR pluripotent OR ICM OR (inner ADJ cell ADJ mass) ADJ ((stem ADJ cell?) OR (stem-cell?)) OR (hEsc? OR mEsc? OR rESC?) OR (hES ADJ Cell?) OR (mES ADJ Cell) OR (rES ADJ Cell) OR (hES-Cell?) OR (mES-Cell) OR (rES-Cell))) AND (PRY>=(2008)) OR (AIC=(C12N00050606)) AND (PRY>=(2008)) ) AND (CTB=((mammal* OR human?)) OR AIC=(C12N000506* OR C12N000516*)) AND (PRY>=(2008))
Electroactive material	(CTB=((("conduct* OR (electro ADJ activ*) OR (electro-activ*)) NEAR4 (*material? OR surface? OR *scaffold* OR foam? OR (biopolymer*) OR (bio-polymer*) OR polymer* OR *fiber? OR *fibrous OR *tubes?))) AND (PRY>=(2008))
Electrical and optical stimulation of cells	AIC=(C12N2529* OR C12N001300) AND (PRY>=(2008)
Self-assembly of cells	AIC=(C12N0005*) AND CTB=(cell? NEAR10 (self ADJ3 (aggregat* OR assembl* OR organis* OR contract*)) AND (PRY>=(2008)
Controlled/induced assembly of cells in response to a stimulus which is electrical or chemical	AIC=(C12N0005*) AND CTB=((cell? NEAR7 (aggregat* OR assembl* OR organis* OR contract*)) NEAR13 ((controlled OR controllably OR stimulat* OR trigger* OR stimuli OR stimulus OR induc*) NEAR7 (electric* OR light OR optic* OR chemical*)) AND (PRY>=(2008))
Scaffold-free artificial tissues or cell aggregates	AIC=(C12N0005*) AND CTB=((((synthetic* OR artificial*) NEAR4 (tissue? OR organ?)) OR (cell? NEAR10 (aggregat* OR assembl* OR organis* OR contract*)) AND (((scaffold?) NEAR5 ("not" OR no OR absen* OR free OR without) OR scaffoldless OR "scaffold-less")) AND (PRY>=(2008))
Controlled/induced gene/protein modifications in response to a stimulus	AIC=(C12N0005*) AND CTB=((((controlled OR controllably OR stimulat* OR trigger* OR stimuli OR stimulus OR induc*) NEAR10 (electric* OR light OR optic* OR chemical*)) SAME (crispr OR cas9 OR ((gene OR dna OR protein OR polypeptide) ADJ (modif* OR alter* OR cleav* OR fusion OR fuse OR cut* OR nick*))) AND (PRY>=(2008))

\* denotes a wildcard, for any suffix or prefix variation when placed at the end or start respectively

## APPENDIX C: TECHNOLOGY ANALYSIS

Patent families relating to mammalian pluripotent stem cells were categorised in to technology groups using Derwent Data Analyser (DDA) auto classification tool. A sample set of patent families falling under each category was identified using keywords based on searching in titles and abstracts, as per the table below and was used to train the DDA classification algorithm. English titles and abstracts and the patent classification symbols of patents applications in the training set were used to train classification algorithm.

Further categorisation was completed using Tableau calculation based on English titles and patent classification symbols. Multiple classification symbols may be present for a single patent family and in categorising patent families overlap where families could be placed in multiple categorises was noted. A patent family will only appear in one category, based on the prioritisation as per the order of the tables below.

Category	Keywords
Stimulation	Electromagnet OR electr* OR light OR shear OR voltage* OR photosensitive OR "physical force" OR pseudo-microgravity (electr* AND active*) adjacent to each other OR conductive OR conductor OR piezoelectric OR infrared OR (electr* AND conductiv*) adjacent to each other
Scaffold culturing	Scaffold* OR bioscaffold* OR nanoscaffold* OR ((self ADJ assembl*) OR "self-assembly" OR "self-assembling" OR "self-assembled") AND (nanostructure* OR peptide* OR compound*) within the proximity of three words OR ((biomimetic OR cultur*) AND support) within the proximity of three words OR decellularized OR decellularised OR "de-cellularized" OR "de-cellularised" OR recellularized OR recellularised OR "re-cellularized" OR "re-cellularised" OR copolymer OR hydrogel OR polymer OR "polypeptide gel" OR alginate
Self-assembly	(Spheroid OR organoid OR aggregat* OR embryoid OR blastocyst OR (organ AND bud) adjacent to each other OR (embryo AND bud) adjacent to each other OR (scaffold ADJ free) OR "scaffold-free" OR scaffoldless) NOT (((self ADJ assembl*) OR "self-assembly" OR "self-assembling" OR "self-assembled") AND (nanostructure* OR peptide* OR compound*)) within the proximity of three words
Differentiation	(Cell AND therap*) adjacent to each other OR (Promot* OR induc*) AND differentiat* within proximity of one word
Disease models	Mouse OR mice OR screen*
Stem cell production	viral OR virus OR (cell AND cultur*) OR ("stem cell" OR ips) AND (produc* OR manufact* OR generat* OR grow* OR isolat* OR obtain* OR reprogram* OR repair* OR purif* OR proliferat*)
Cryopreservation	Cryopreservat* OR preservat*

\* denotes a wildcard, for any suffix or prefix variation when placed at the end or start respectively

## APPENDIX D: PATENT STATUS DETERMINATION

DWPI database defines the status of a patent (Dead/Alive Status) based on two factors: expiration date and terminal legal status events (failure to pay maintenance fees or revocation). Patents with no terminal events within their predicted term are categorised as 'Alive', patents with terminal events or that reach their expiration dates are categorised as 'Dead' and those without expiration and legal status data are categorised as 'Indeterminate'.<sup>50</sup>

The granted status of a patent application was determined using 'INPADOC Legal Status' and 'Publication Kind Code' details relating to that application available in DWPI database.

A patent family is considered 'Granted' if 'INPADOC Legal Status' / 'Publication Kind Code' indicates that at least one family member was granted in any of the jurisdictions. If there are no 'Granted' family members and 'Dead/Alive Status' indicates that at least one family member is 'Alive' or 'Indeterminate', then that family is considered as protection 'Being sought'. A patent family is considered 'Dead' if none of the family members are granted and 'Dead/Alive Status' indicates that all family members are 'Dead'.

<sup>50</sup> Derwent Innovation Predictive Data Patent Status (Dead or Alive), [https://clarivate.com/wp-content/uploads/2017/10/di\\_info\\_doa\\_en.pdf](https://clarivate.com/wp-content/uploads/2017/10/di_info_doa_en.pdf)

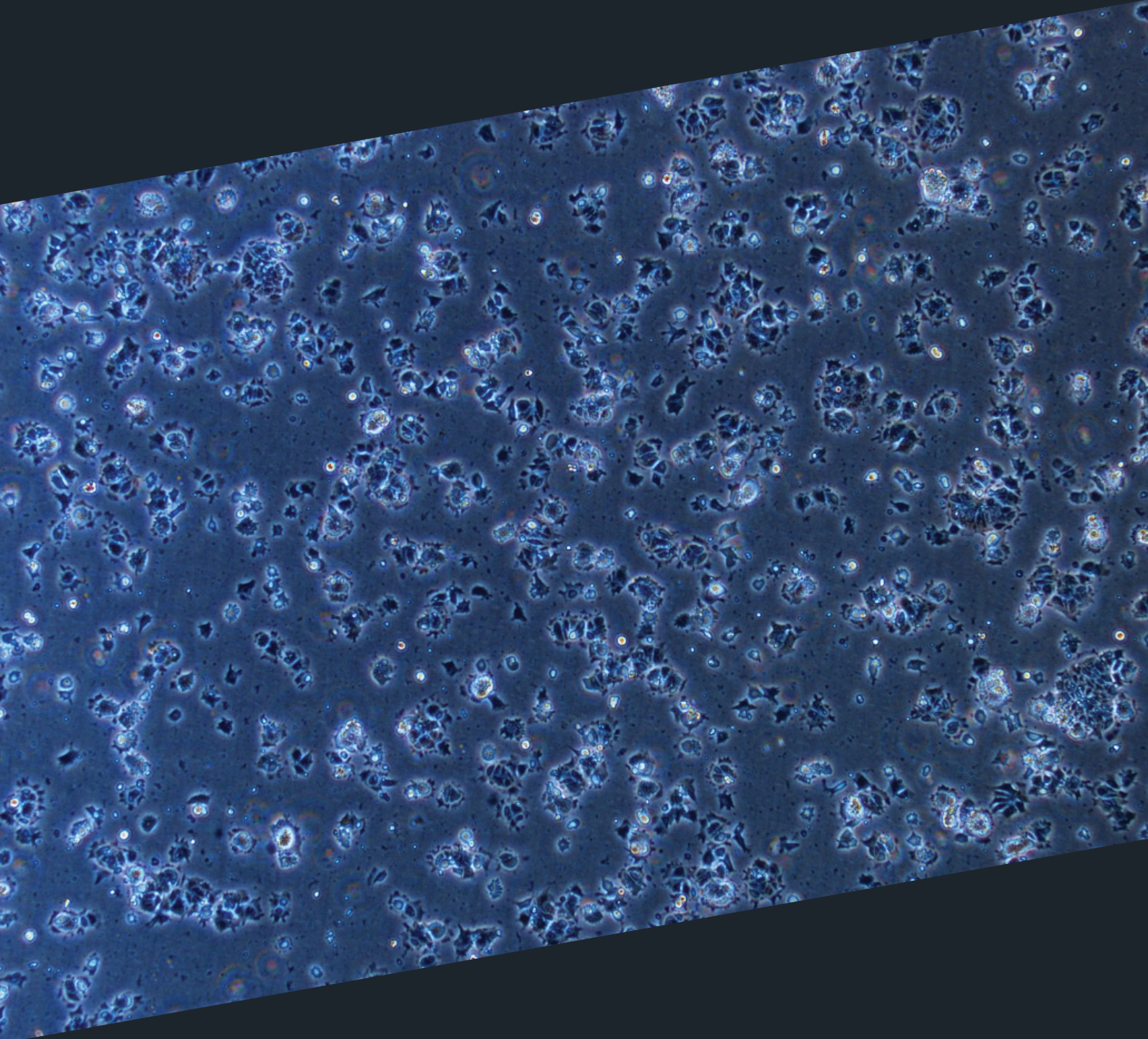


Image of cells by researcher Nadia Rajab, University of Melbourne