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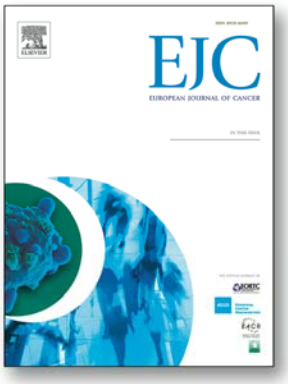

EUROFILE

Concern over possible impact of hESC Ruling

A ruling from the Court of Justice of the European Union (CJEU) on the use of human-embryo derived stem cells could have long term consequences for biomedical research, an expert has warned.

While cancer researchers remain less concerned than their colleagues in regenerative medicine, Aurora Plomer, Professor of Law and Bioethics (University of Sheffield, UK) believes that the implications of the ruling are widespread.

"Most of the research on human embryonic stem cells is at a very basic level: understanding how cells develop, how they multiply, and how they can be controlled not to multiply, so it's highly relevant to cancer," she says.

Research using hESC is less tightly regulated in the USA than in Europe, where in November 2011 the CJEU upheld Greenpeace's challenge to a patent held by Oliver Brüstle, Director of the Institute of Reconstructive Neurobiology, Bonn, to protect a method of transforming hESCs into neurons. In its judgment, the CJEU ruled that such procedures violated existing restrictions (Directive 98/44/EC) on the industrial or commercial use of human embryos.

The Ruling states that where the implementation of an invention requires the use of cells that originate from a process which requires the destruction of a human embryo, the invention is not patentable, even if the claims of the patent do not refer to the use of human embryo.

> ***'This Ruling could have a huge impact on all downstream research. It precludes patents on 2nd or 3rd line derivations from the original stem cells'***
>
> **Aurora Plomer, Law and Bioethics, University of Sheffield, UK**

In the UK, which is among those EU countries with the greatest number of projects involving hESCs, a House of Lord's publication in July 2013 reported "significant concerns" about the CJEU Ruling. The report, *Regenerative Medicine*, by the Advisory

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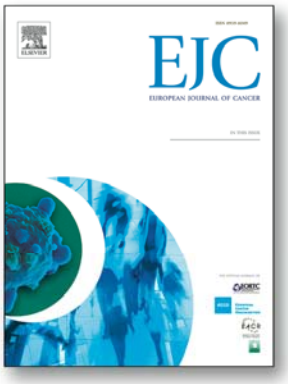

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Committee in Science and Technology, cited a “lack of clarity” and “uncertainty”.

Advisor to the report, Fiona Watt, Director of the Centre for Stem Cells and Regenerative Medicine, (King’s College London, UK), says opinions vary on how deleterious the CJEU Ruling was.

“I think everyone agrees that in that technical area, any practical application of a stem cell derived from an embryo would probably be covered by multiple patents and would rely heavily on technical know-how,” Professor Watt says.

Steve Pollard, (Samantha Dickson Brain Cancer Unit, University College London, UK), says: “Human embryonic stem cells potentially provide a useful experimental tool to generate large quantities of normal human cell types that might not otherwise be accessible. These could then be used to explore how oncogenes and tumour suppressors affect their behaviour,”

> ***‘Patents are an important aspect of attracting investment, but stem cell research is so complicated that 'know how' might be just as valuable as patents’***
>
> **Steve Pollard,**
> **University College London, UK**

However, Pollard, who investigated the conversion of embryonic stem cells to neural stem cells with Austin Smith (Institute for Stem Cell Research, Edinburgh, UK) says that tissue stem cells are much more valuable:

“Genes and pathways that are used by normal tissue stem cells may represent useful 'biomarkers' to understand the grading and prognosis for patients with a specific tumour type.”

They also represent new types of therapeutic target: “Epigenetic machinery that sustains cells in perpetual cycles of self-renewal, blocking differentiation, may represent new useful drug targets,” he says

Pollard is currently using reprogrammed glioblastoma stem cells in research on brain tumours. “We have used iPS technology to reset the epigenetic abnormalities in glioblastoma (GBM). We compare GBM stem cells to normal neural stem cells and then define 'aberrant' epigenetic marks. The reprogramming procedure erases the epigenome and then this can be reset to the neural lineage again through in vitro 'redifferentiation'. By doing this we essentially 'rebooted' the cancer cells. This has given us insights into the relative importance of epigenetic and genetic pathways for this particular cancer.”

Dr Pollard is not unduly concerned about the effect of the CJEU ruling preventing

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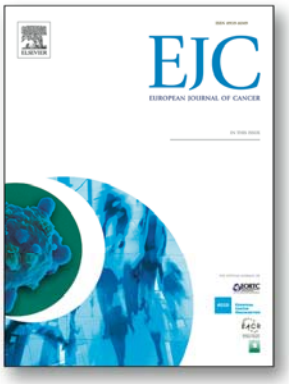

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patents been taken out on any product derived from research using hESC lines. "While patents are an important aspect of attracting investment, stem cell research and regenerative medicine is so complicated that 'know how' might be just as valuable as patents."

But Plomer said, "This Ruling will potentially have a huge impact on all downstream research on human embryonic stem cells. "The position adopted by the European Court of Justice precludes patents not just on embryonic stem cells but on the 2nd or 3rd line derivations from the original stem cells, It affects any further uses of those cells irrespective of how far downstream that may be in terms of a therapy or a product that is developed.

"People are saying that they could patent things like the platforms the cells were grown on, devices and various other things, and that they can keep everything secret, she says. "But no product or therapy can be patented that involves these cell lines so this could be a serious turn-off for investors in Europe."

A lack of scientific understanding among the judges comprising the court is part of the problem, according to Plomer who pointed out that hESCs created artificially by parthenogenesis were covered by the Ruling.

"It makes you wonder about the Judges personal competence and bias," she says, "National Courts are not bound by a Ruling of the European Court of Justice when the Court has erred on a point of fact."

> ***'Any practical application of a stem cell derived from an embryo would probably be covered by multiple patents and would rely heavily on technical know-how'***
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> **Fiona Watt,**
> **King's College London, UK**

International Stem Cell Corporation (ISCO), which is based in California, has won an appeal through the UK High Court against the previous rejection of a patent application for its methods of obtaining human stem cells derived from oocytes stimulated by parthenogenesis

The Judge, Henry Carr, QC, has referred the case to the CJEU, seeking clarification as to whether unfertilised human ova whose division and further development have been stimulated by parthenogenesis, and which, in contrast to fertilised ova, are incapable of developing into human beings, are included in the term 'human

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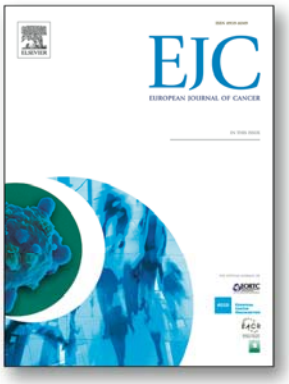

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embryo' under Article 6(2)(c) of the Biotechnology Directive.

Simon Craw, Vice President, of ISCO, says: "It is important our patent application is successful as we obviously want to protect our invention in the EU.

"It's critical for companies to be able to protect themselves and get a return on the investment they have made in developing new technologies," Craw says. "Developing a cellular therapeutic product from a stem cell source is a complex, expensive and time-consuming process. Biological science, including regenerative medicine is truly a global industry, if companies are inhibited from protecting their inventions in Europe then they will simply go elsewhere."

Craw points out that While US Federal funding of hESC research is fairly limited, States such as California, through the California Institute for Regenerative Medicine, have committed billions of dollars to R & D in this area.

He disagrees with the view that patenting holds back research by walling off whole areas: "Patenting puts technology into the public domain in a sense; it allows other people to use it, licence it or get ideas from it. A patent helps innovation; it gives multiple incentives for people to find a way around it, and it gives people a platform to build on."

> ***'Patenting puts technology into the public domain; it helps innovation; incentivises people and gives them a platform to build on'***
>
> **Simon Craw, International Stem Cell Corporation, USA**

The CJEU response to the ISCC appeal could take up to a year.

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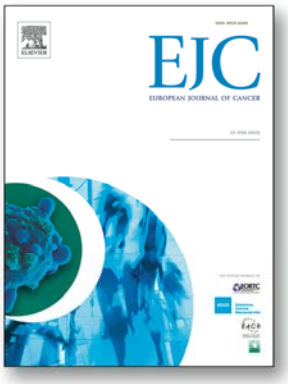

INTERVIEW

Time to rethink trial eligibility criteria?

The list of possible reasons for patients' exclusion from clinical trials has become exhaustive. Typically, trial patients are younger than those seen in routine practice; they have better performance status and less co-morbidity. Increasingly, they may bear little resemblance to patients seen by clinicians on a daily basis.

A Canadian group explored how far patients who do not meet trial criteria may still benefit from treatment. A retrospective study presented at this year's ASCO (Abstract #6502) included 820 patients diagnosed with stage III colon cancer between 2006 and 2008 at one of 5 regional centres in British Columbia. Researchers found a 5 year overall survival rate of 74% among patients who met trial criteria and had received adjuvant chemotherapy. This compares with 65% among those who were ineligible but had still received chemotherapy, and 35% among those who had not received the treatment.

***Winson Cheung (British Columbia Cancer Agency)** led the study and suggested that more flexibility is needed in designing eligibility criteria to ensure that trial participants become more representative of the general patient population.*

There were a lot of ineligible patients; more than half of the group as a whole?
That's right; clinical trials have strict criteria and typically select the fittest and most compliant people, i.e. the 'best' patients. In routine practice, a lot of the people we see are not as fit, so the question is: how do clinicians apply results from fit clinical trial populations to those we see on a daily basis?

Which criteria cause most exclusions?
Most inclusion/exclusion criteria are patient factors rather than measures of disease. Most trials, for example, choose people who are less than 70 years old and who have a performance status of 0-1. In routine practice, we see some patients like this, but a large majority are over 70, with a performance status worse than 1. I think we should rethink eligibility criteria to become more flexible and open to other patients being included because we are treating these less fit people in real life.

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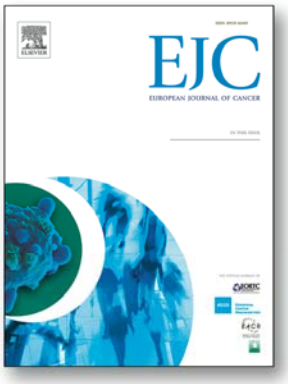

Winson Cheung *continued.*

As things stand, best clinical practice might involve treating people outside of standard indications?
This happens quite frequently. Say a trial doesn't include anybody over 70 and in my clinic I see someone who is 71 and otherwise fits all of the remaining criteria. A purist would say this 71 year old should not receive treatment, but many clinicians would still treat.

Is there any way around that?
There is a lot of interest in using different tools to assess biological age, so one strategy to broaden clinical trial criteria might be to use an assessment tool to hone in on the person's true biological age. There are ways to fine tune what we are doing right now, and such tests would at least reassure us that we are doing our best to accurately describe and evaluate the individual patient. A limiting factor is that these assessments are labour intensive and time consuming to carry out, so they might not be feasible in all clinics but it would be good to have some sort of evaluation algorithm to decide who is fit enough to be included in a trial.

Did you suggest that patients' compliance can determine their inclusion?
Compliance is not typically included as an eligibility criteria, but when a patient is considering entering a trial, I want them not only to fit the stated criteria, but I'm also looking for some suggestion that they will adhere to the treatment schedule, come back for appointments, abide by the instructions, and so forth. If someone fits the criteria but is not conscientious at all about the study requirements, then I would have reservations about enrolling that person because s/he would jeopardise the integrity of the trial.

Does education level come into it?
Education is not on the criteria list, but most trials have detailed consent forms; studies have shown that they are typically written at the high school level. As such, they may exclude people without that level of education. People of lower socio-economic status tend to not participate in trials as frequently as those who are highly educated. We don't want to exclude people on these grounds, but it is sometimes unfortunately hard to avoid because of the way trials are designed.

What are the main implications of your work?
Trial ineligible patients are often sicker and less fit, so I expected that their outcomes would be worse than those who were eligible and received chemotherapy. At the same, there appears to be some benefit in treating certain ineligible people since they still did better than those who were ineligible and did not get chemotherapy. These results do not imply that all ineligible people should get treatments though. If the only reason why someone is ineligible is age, that is very different from someone who is ineligible because of kidney problems, heart trouble, or high cholesterol. The take-home message is that some – but not all – ineligible people might benefit from chemotherapy. So, it begs the question of whether we should modify future clinical trial eligibility criteria to be a little more inclusive.

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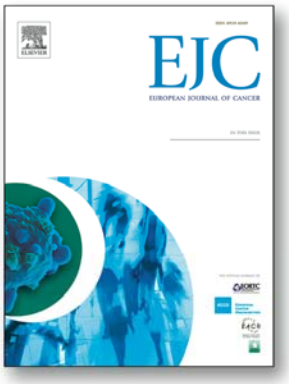

Winson Cheung *continued.*

Should eligibility criteria be different in trials of targeted and more personalised therapies?

I foresee the criteria being different, although this does not necessarily mean stricter. In a trial of a chemotherapy agent that is known to cause kidney problems, for example, it makes sense for kidney function to be included in the exclusion/inclusion criteria. Many targeted agents have specific toxicities, so the exclusion criteria need to be tailored to that particular medication. If a drug has significant toxicity in the elderly, there's an argument for an age cut off, but if it's a medication with few side effects, then the patient's age is probably less relevant. It will be up to investigators to design unique criteria for each trial and decide which factors really matter. There are no one-size-fits-all criteria.

Interview by Helen Saul

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