International Regulatory Forum of Human Cell Therapy and Gene Therapy Products

MHRA
Regulating Medicines and Medical Devices

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JSRM
The Japanese Society for Regenerative Medicine

一般社団法人
日本再生医療学会

AMED
Japan Agency for Medical Research and Development

NIBIOHN

Medicines and Healthcare Products Regulatory Agency

Preclinical safety evaluation

JW McBlane PhD
16 March 2016

Osaka

Medicines and Healthcare Products Regulatory Agency

Disclaimer statement

Any views expressed are my own, are not views of the MHRA (Medicines & Healthcare Products Regulatory Agency), the CAT (Committee for Advanced Therapies) or the EMA (European Medicines Agency) and should not be represented as such.

Overview

Preclinical safety studies for human cell therapy and gene therapy

When are studies not required?

When studies are required, what might be suitable?

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Jane Austen
Pride and Prejudice (1813)
Chapter 54

JW McBlane – summary

PhD pharmacologist

13 years in pharma industry (10 with Chugai in Europe)

13 years as an assessor at MHRA (where I am now)

3 years as UK *alternate* delegate to the European Medicines Agency's Committee for Advanced Therapies (EMA/CAT)

In my day-to-day job, I:

- assess applications for UK clinical trials & EU marketing authorisations
- give scientific advice on behalf of MHRA and CHMP/EMA

I am interested in the question: what does the drug do?

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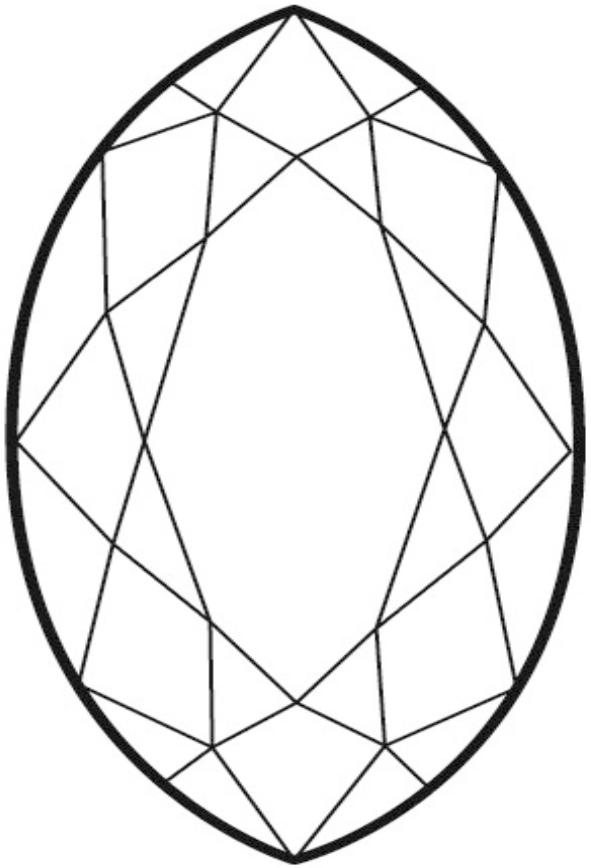
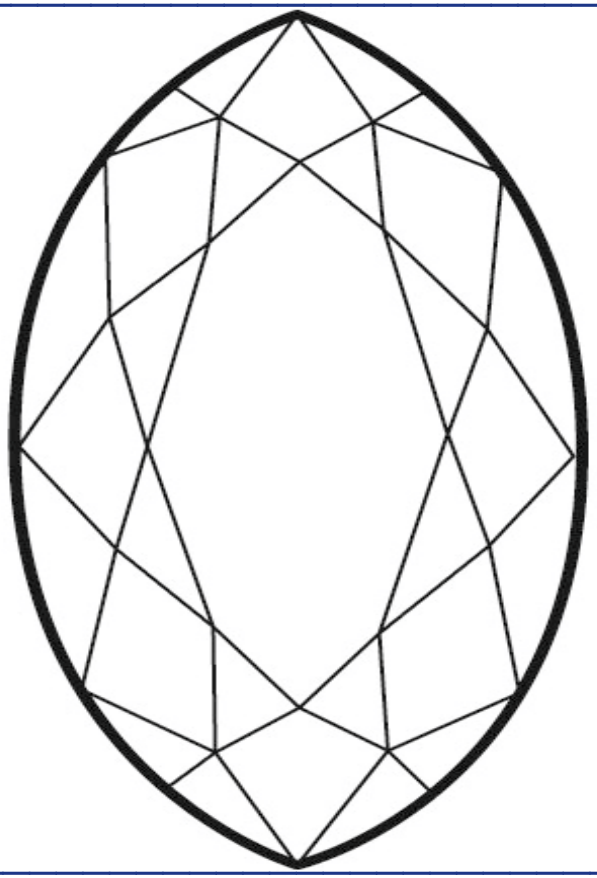


no preclinical (safety) testing



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When are preclinical safety studies not required?

- where there are already sufficient clinical data to obviate need for further (or any) preclinical testing

- where such testing would not be relevant

Sufficient clinical data - example

HOLOCLAR – Chiesi Famaceutici (Parma, Italy) (conditional approval)

-autologous stem cells to replace damaged corneal epithelia due to limbal stem cell deficiency (eg after burns)

-corneal epithelial cells with 3.5% limbal stem cells

-acts to replace the corneal epithelium and supply limbal stem cells

Sufficient clinical data – example - Holoclar

Non-clinical toxicology assessment of Holoclar was limited and abridged, as was justified by the applicant by the already existing clinical experience with the product as well as the lack of relevant animal models due to differences in the structure of most other mammals

Potential for transformation *was* assessed by in vitro methods – karyotype analysis & growth potential in soft agar

(EMA, EPAR)

Sufficient clinical data – example - Holoclar

Holoclar had been used in ~200 patients prior to the introduction of the ATMP legislation in Europe

Conduct of retrospective preclinical safety studies was deemed not appropriate

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Studies not relevant …

World first use of gene-edited immune cells to treat 'incurable' leukaemia
05 November 2015 Great Ormond Street Hospital, London

Press Release

'*A new treatment that uses 'molecular scissors' to edit genes and create designer immune cells programmed to hunt out and kill drug resistant leukaemia has been used at Great Ormond Street Hospital (GOSH). The treatment, previously only tested in the laboratory, was used in one-year-old, Layla, who had relapsed acute lymphoblastic leukaemia (ALL). She is now cancer free and doing well*.'

http://www.gosh.nh-first-use-gene-edited-immune-cells.uk/news/press-releases/2015-press-release-archive/worlds-treat-incurable-leukaemia

CAR T cells

Autologous or allogeneic

T cells + vector leading to expression of chimaeric antigen receptor

-so bringing target specificity to T cells
-target a cancer-related antigen
-or an antigen on the cancerous cell type

•‘Chimeric antigen receptor’ returns >3100 hits on PubMed
•58 with limit ‘clinical trial’

CAR T cells

Lack of

•‘acute & chronic toxicology

•safety pharmacology

•genotoxicity

•carcinogenicity

•reproductive and developmental toxicity

•and immunotoxicity

as this is a trial of a genetically-modified, autologous cellular therapy’

CAR T cells

- do not target an antigen present in healthy animals

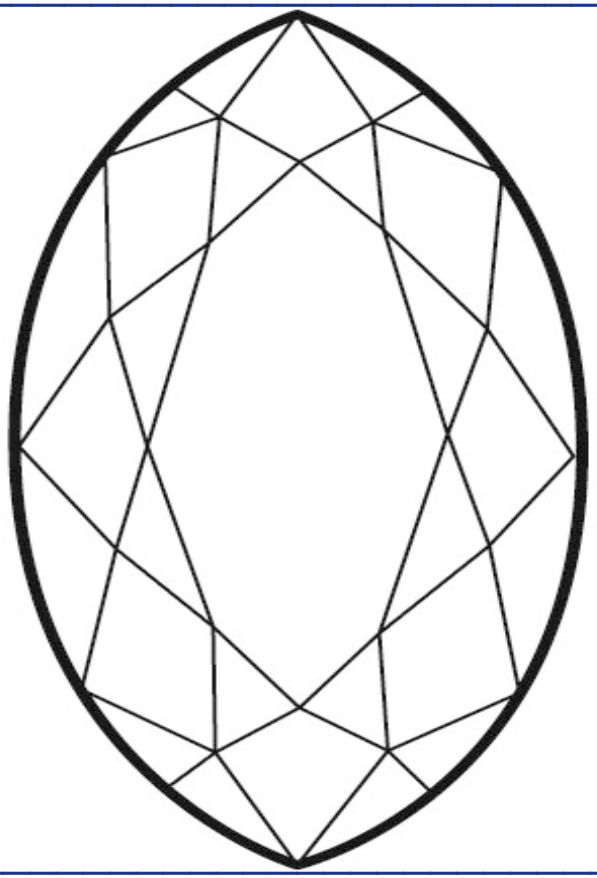
- may be specific to human antigen or to an antigen expressed (only) in human disease

- preclinical safety studies in normal animals do not reflect the intended pharmacological effect of the genetically modified cells

- can do proof of concept studies in (immunodeficient) animals xenotransplanted with human tumour then given the human cell product – highly complex

no preclinical (safety) testing

preclinical (safety) testing



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No preclinical safety testing

- autologous cells subject to minimal manipulation but used in a non-homologous setting

- no ex vivo expansion step – eg purely cell purification

- cells not intended to be used for the same essential function between recipient and donor (see EMA/CAT/600280)

- noting that this is not always so easy (see Jane Austen …..)

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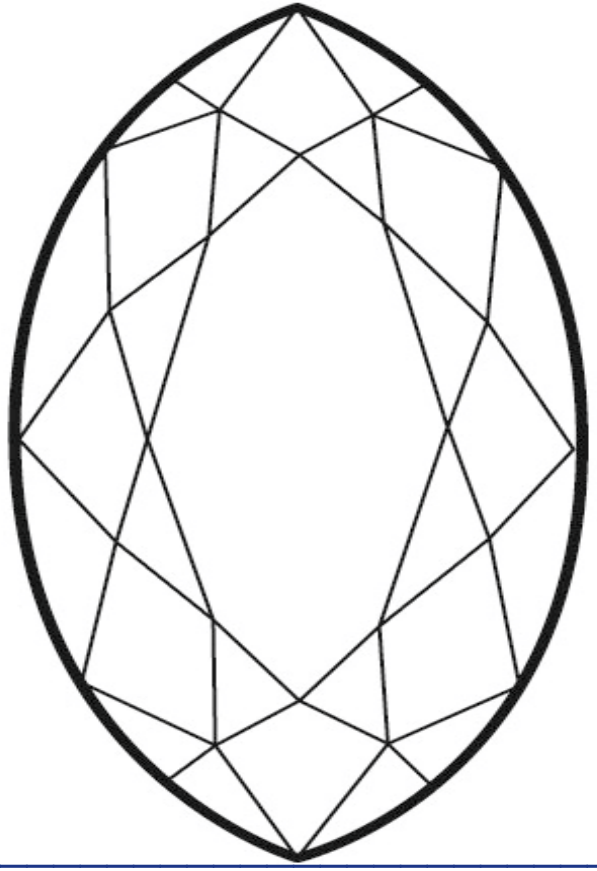

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Preclinical safety testing

- required where studies are considered relevant to human use
- animal species show sufficient similarities to human situation for testing to be considered predictive for human
- there may be the possibility of including safety assessment in proof of concept studies or in biodistribution studies
- role of in vitro testing methods
- consider multiple aspects of design of in vivo study

Consider multiple aspects of design of in vivo study

- choice of species – one can suffice but more than one might be better

- nature of the animal – should it be immunocompetent but given immunosuppression or immunodeficient & if so, which type?

- consider safety of the process of administration and device – integral to how the product is to be used in humans
  - this may influence the 'treatment' of controls – eg needle inserted but nothing delivered, sham injection, effect of injection volume separate from effect of cells ..

- nature of the product used – human cells representative of the finished product? animal cells?

- conduct under Good Laboratory Practice if feasible

Consider multiple aspects of design of in vivo study

- single or multiple doses?

- are multiple endpoints – biodistribution, persistence and safety - included in one study?

- nature of the animal - II – diseased or healthy?
  - the disease process may influence the environment into which the cell product is given so affecting retention / activation of the cells

In vitro testing for tumour risk

- need for testing depends on differentiation potential of cell therapy
- use of growth factors in cell production?

- genomic testing of clinical batches used in development

- do cells reach senescence in vitro - population doublings?

- karyology – chromosomal number and appearance – length, centromere position etc

- judgement on additional testing where abnormalities found – eg telomerase RT testing

Summary so far

- preclinical testing is done to support later clinical testing & use
- for some products, there is no relevant in vivo preclinical testing
- testing may address proof of concept – distribution / persistence – and safety in studies assessing more than one of these elements
- testing should include the consequences of how the product is given – this is a separate concept from the assessing the cells' potential effects – eg volume injected
- in vitro methods may complement in vivo testing now – in the future?

Time for an imaginary example?

Imaginary example

- cell therapy for use in patients with dementia of Alzheimer's type

- allogeneic neural stem cell

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- tested in proof of concept studies in mice with cognitive deficits
- eg APP23, TG2576

- cells injected into mouse brain resulted in improvement in performance in tasks on a radial arm maze and in location of platform submerged in water (Morris maze)

- mice given cell product 'remember' better and have shorter times to reach end of test (find reward at the end of one arm, or get to the platform)

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What preclinical safety testing is expected?

Some themes:

-What is the mode of action of this product?

- is it cell replacement in the longer term?

-What evidence would support this?

- testing for human cells in mouse brains at eg 1 day, 1 month and 6 months post dose
- do these human cells form networks through other regions of the brain?- neuroanatomical investigations

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-do such data suggestive that the same might happen in patients?

-is it possible / sensible to select a human dose based on animal data?

Some themes

- Persistence in context of safety assessment

- there could be long term benefit in the mice either with long term cell persistence or without long term cell persistence

- if cells are not detectable in mouse brain after, say 14 days, what are the implications for longer term safety studies in mice?

- if the cells are present/absent in mice at 6 months what is the significance of this for licensing? – mode of action and safety

Some themes

- Persistence linked to distribution
- would these cells distribute systemically?
- are considerations different for this population?

Some themes

- General toxicity testing

- mice only probably not sufficient due to delivery considerations
- second species not showing any dementia deficit?

or

- use of a vascular insult to induce cell death to mimic vascular dementia and so facilitate cell retention?

- use of immunosuppression in these animals and impact on clinical study – should patients be tested +/- immunsuppression to see if there is any apparent difference?

- does the age of patients influence tumour risk assessment eg timing of preclinical study in relation to clinical use?

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[ENDS

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THANKS]