Potency assay development for cellular therapy products:
an ISCT review of the requirements and experiences in the industry

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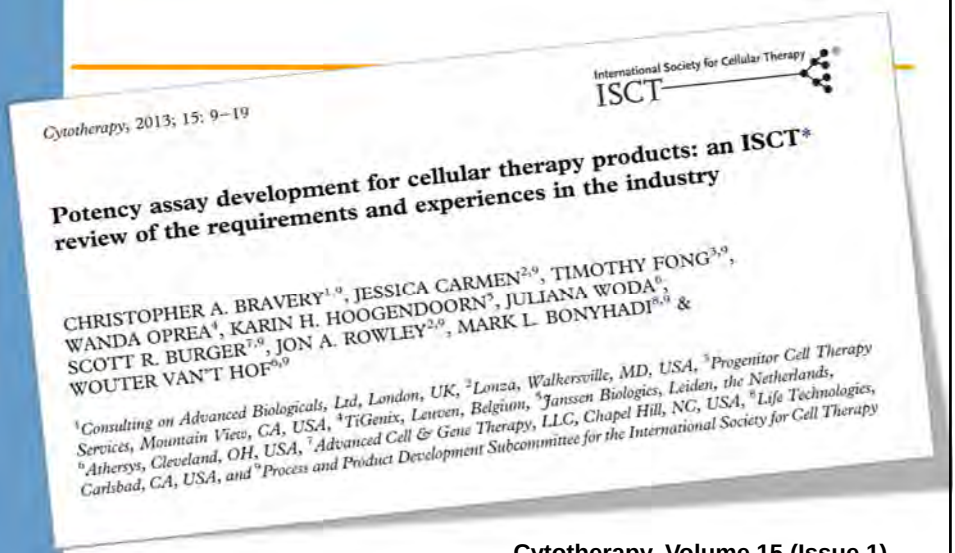

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International Society for Cellular Therapy ISCT

Potency assay development for cellular therapy products: an ISCT* review of the requirements and experiences in the industry

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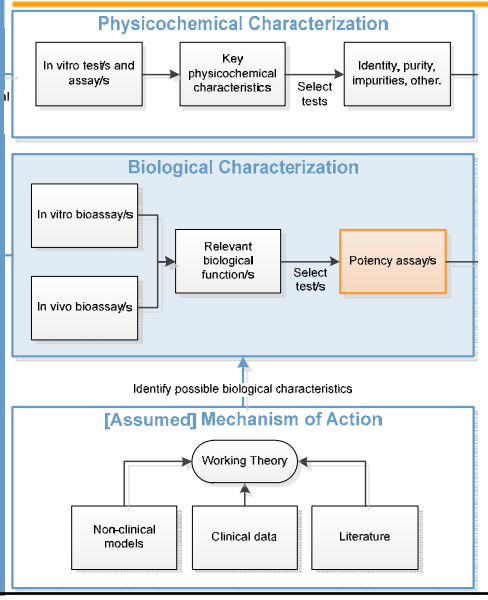
Paper Outline

- Characterization
- Why is potency so important?
- Regulatory expectations for CTPs
- Potency assay strategy for CTPs
- Practical considerations
- Reported potency assays in the field and case studies

Characterisation Strategy



Physicochemical characterization
Refers to the use of methods that measure physical and chemical characteristics. Eg:
Physical: size, morphology, light scattering properties, tensile strength, cell number, confluence.
Chemical: identification of phenotypic markers and secreted substances, genotype, gene expression profile.

Biological characterization
Refers to the use of methods that measure biological function, i.e. how the physicochemical characteristics influence biological systems. Eg:
Biological: *in vitro* and/or *in vivo* measurements of cytotoxicity, cell growth, de/differentiation, proliferation, migration, immunomodulation.

What is a potency assay?

- Biological ‘activity’ implies a change over time; so single measurements are not biological assays.
- Any assay used for biological characterisation could be a potency assay if it gives a meaningful indication the product will be ‘potent’.
- It is unlikely one single assay will capture all biological effects.
- One or more biological assays may be needed together to define potency.
- Biological characterisation will allow you to identify which assays are candidate ‘potency assays’

Selecting a potency assay?

- Practicalities will necessarily limit those that could be used for product release, e.g. An in vivo assay (e.g. Botox) is unlikely to be possible for cell therapy release testing.
- Where time or material mean a true potency assay would not be possible, a surrogate measure can be used, e.g.
  - ChondroCelect – expression of gene markers
  - Provenge – Expression of CD54

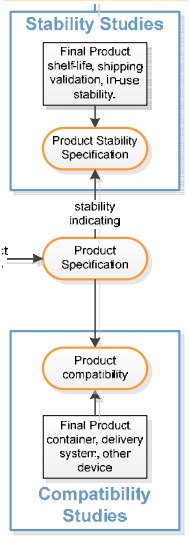
Warning!

- These surrogates for potency are only valid if correlated to other bioassays and/or *in vivo* effects relevant to the MoA.

Examples of Potency Assays

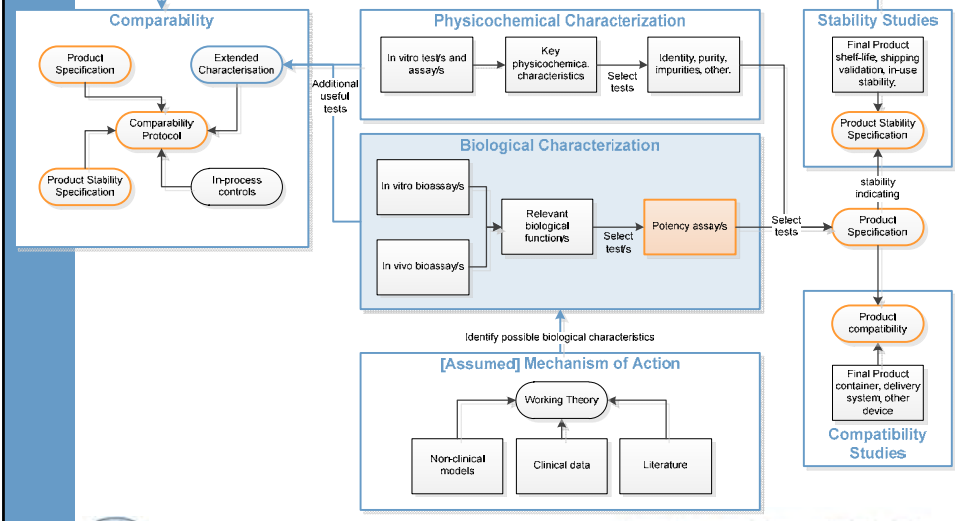
	Platform	Indication / Status	Potency Assay	References
Autologous	ChondroCelect (TiGenix). Autologous chondrocytes	EMA Approved knee cartilage repair	Expression of molecular markers (PCR)	*Supplemental Information*
	PROVENGE®, sipuleucel-T (Dendreon). Primed, expanded T cells	FDA Approved, treatment of hormone refractory prostate cancer	CD54 expression (FACS)	(12)
	Xcellerated T Cells (Xcyte Therapies). Activated T cells	Phase I/II, treatment of chronic lymphocytic leukemia	CD154 expression (FACS)	*Supplemental Information*
	AMR-001 (Amorcyte). Bone marrow derived cells	Phase I, cardiac repair after myocardial infarct	*In vitro* migration of CD34 /CXCR4 cells in SDF-1 gradient	*Supplemental Information*
	Natural Regulatory T cells (Athelos). Ex-vivo expanded nTregs	Pre-clinical, treatment of graft versus host disease	Suppression of CD69 and CD154 in T cell activation assay (FACS)	*Supplemental Information*
Allogeneic	Prochymal (Osiris). Adult stromal stem cells	Phase III, treatment of GvHD	Secretion of TNFR1 (ELISA)	(13, 14)
	Multistem® (Athersys). Bone marrow stromal stem cells	Phase I, treatment of ischemic cardiac disease	Secretion of VEGF, IL8 and CXCL5 (ELISA)	(15)
	GRN-001 (Geron). hES derived oligodendrocyte progenitor cells	Phase I, spinal cord repair	Secretion of neurotrophic factor panel (ELISA)	(16)

The Importance of Potency



- You cannot confirm stability without a potency assay
  - Biological function may be lost before viability
- Viability alone doesn't confirm the product is effective, you need a potency assay.
- Compatibility of the product with devices (e.g. syringes, containers, etc) or other biomaterials (or potentially drugs) cannot be confirmed without a potency assay.
  - Although generally minor issue

The Importance of Potency



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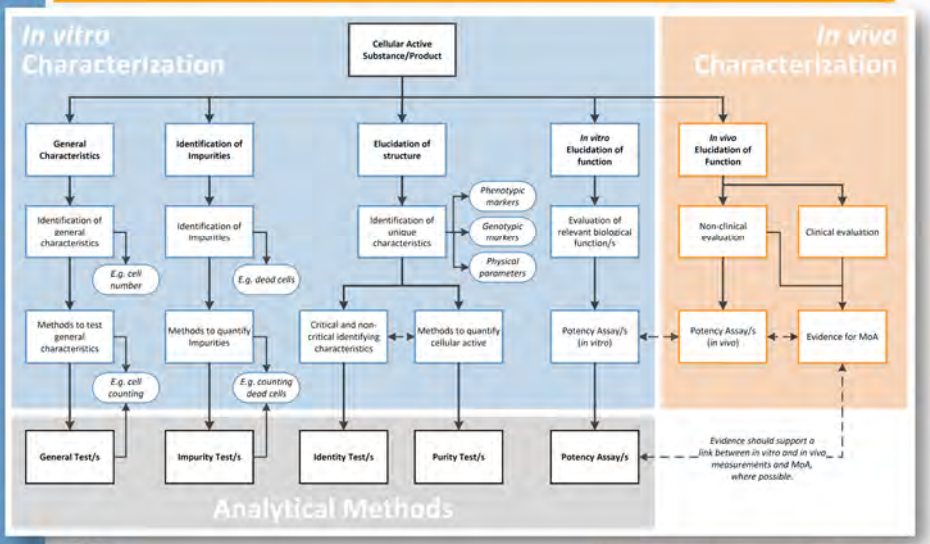
More Reviews to Come…



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Conclusions

- A thorough characterisation program will yield all the tools necessary to control the quality of the CTP.
- Biological characterisation should focus on all the possible MoA
- Thorough biological characterisation should identify potential potency assay candidates
- Surrogate measurements of potency using physicochemical measurements can be acceptable but only when supported by true potency assays, *in vitro and/*or *in vivo*.

Further Reading

- PAS-83 (BSI, 2012) Developing human cells for clinical applications in the European Union and the United States of America. Guide.
  - http://shop.bsigroup.com/en/forms/PASs/PAS-83/ (free download)
- PAS 93 (BSI, *2011*) Characterisation of cells and cell products
  - http://shop.bsigroup.com/en/forms/PASs/PAS-93/ (free download).
- PAS 84 (BSI, 2012) Cell therapy and Regenerative medicine glossary
  - http://www.futuremedicine.com/doi/pdfplus/10.2217/rme.12.38 (free download)

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