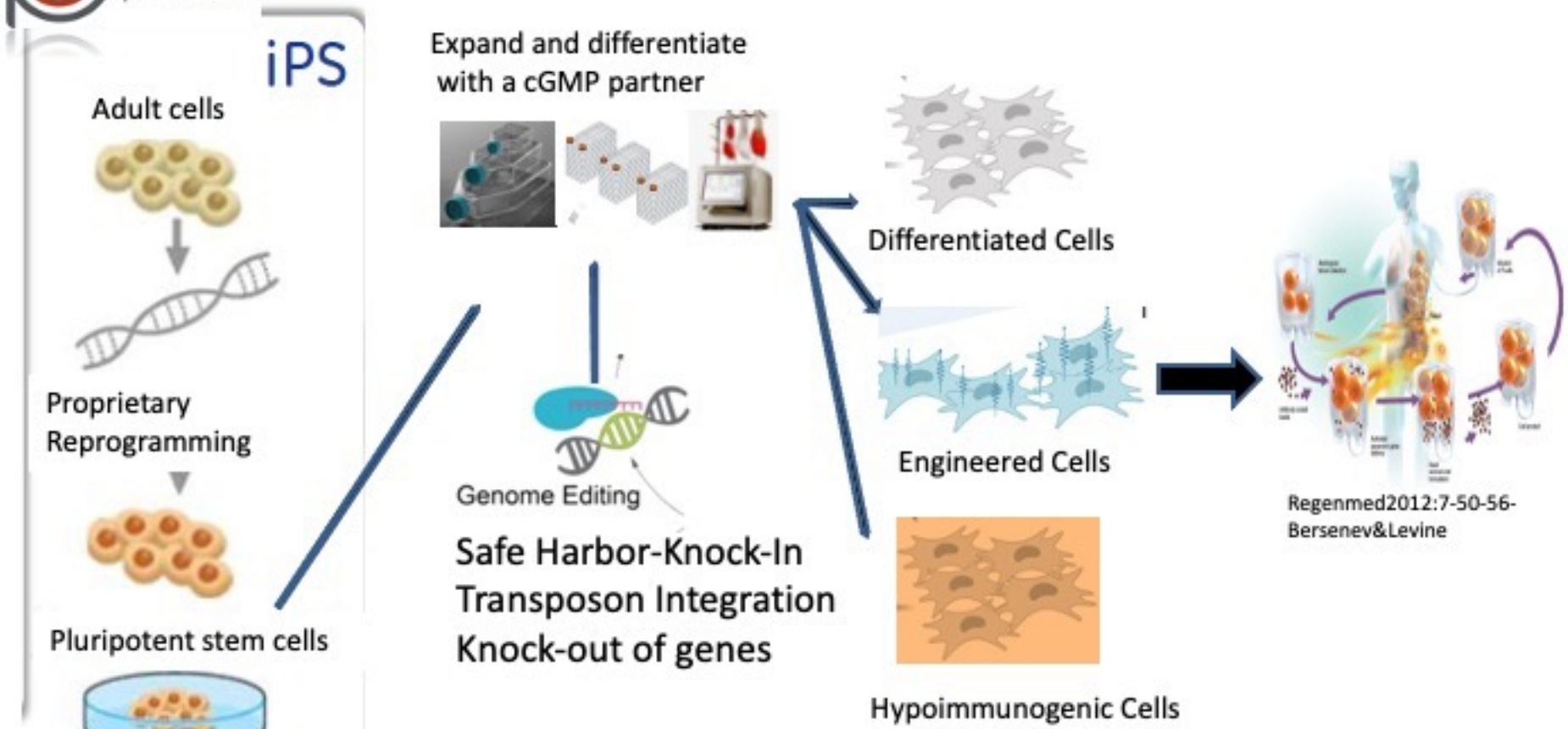
Non-Confidential Slide Deck

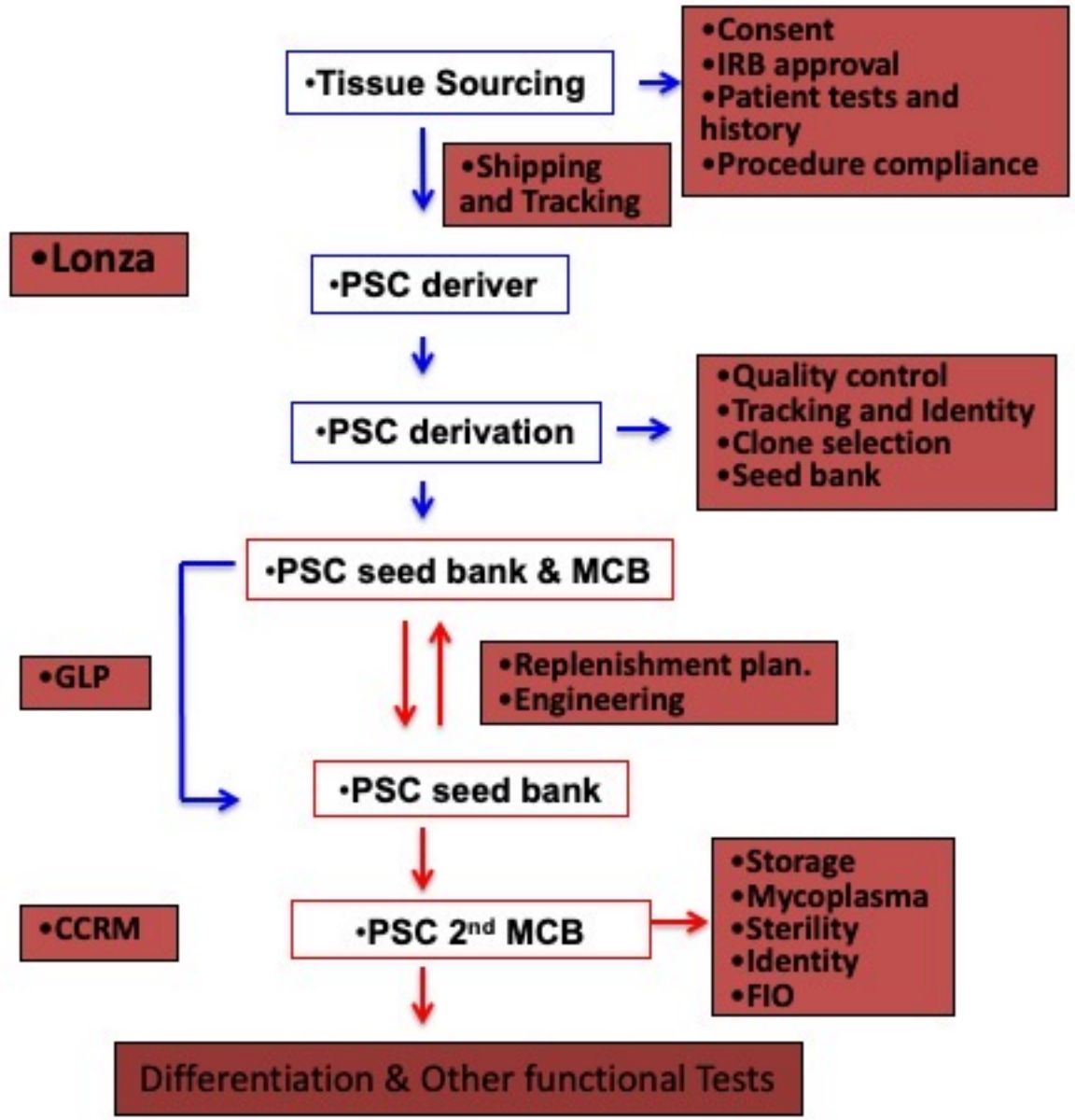
Our Goal- iPSC derived Allogeneic therapy



Success Requires

Developing a cGMP MCB
Having the ability to differentiate to an appropriate phenotype
Having the ability to gene edit (knockout and Knock-in
Having the ability to make Allogeneic transplantable cells (hypoimmunogenic)
All of the above with patent protection and licensed IP for Freedom to Operate

Our Licensed Technologies- IPSC Line (s)



PanCELLa has made three line

PanCELLa can make additional lines

Lines have FTO

Line 1 episomal vector , MCB made

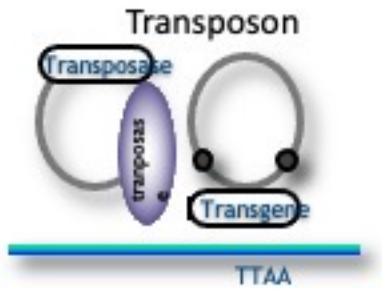
Line 2 RNA virus, Seed bank in progress

Line 3 RNA technology Seed bank in progress

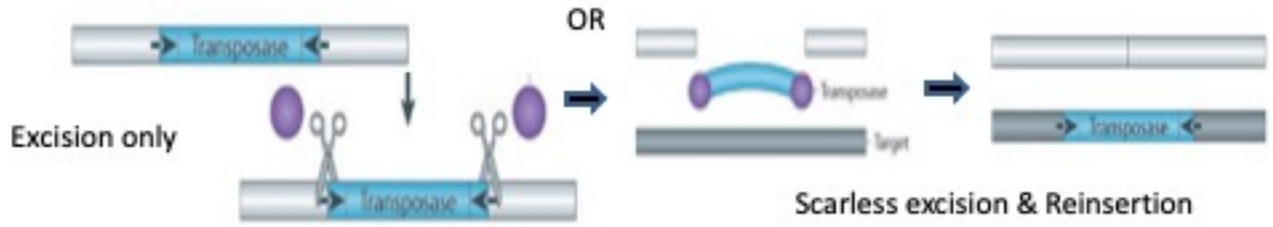
Line 4- Bioproduction Use- MCB ready to be made

Our Licensed Technologies

Piggy-Bac, SB

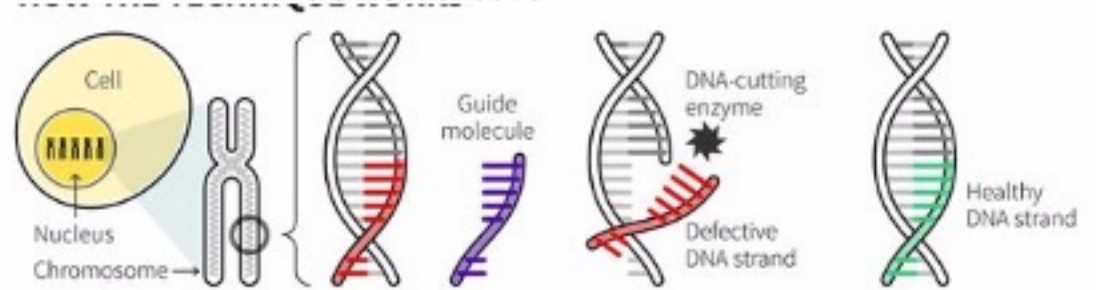


Transposases

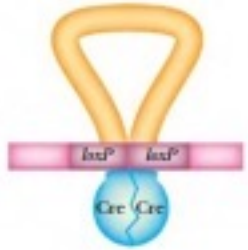


Dualase

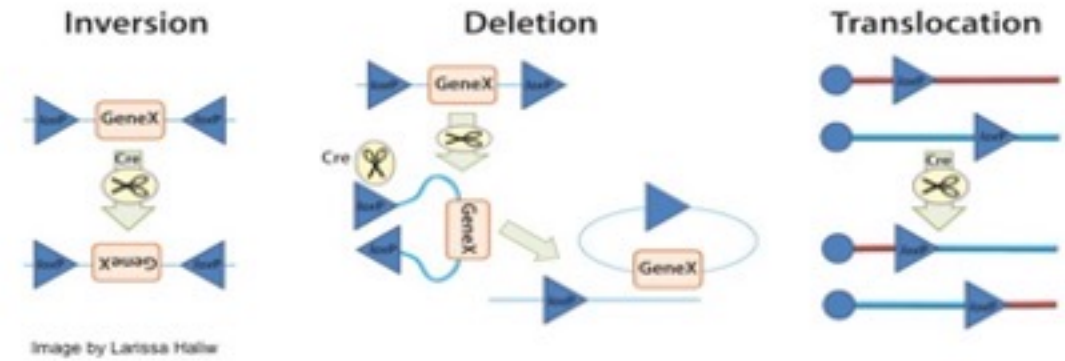
Gene Editors



CRE/FRT

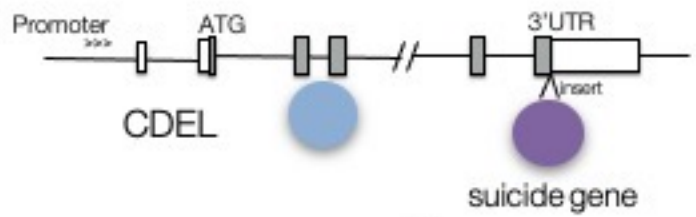


Recombinases



Our Patented Technologies- FailSafe

Edit a Cell division essential locus (CDEL)

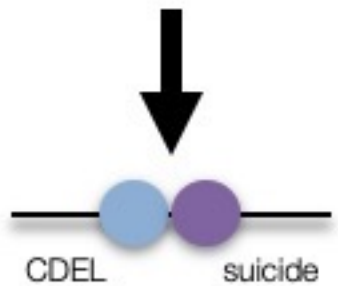


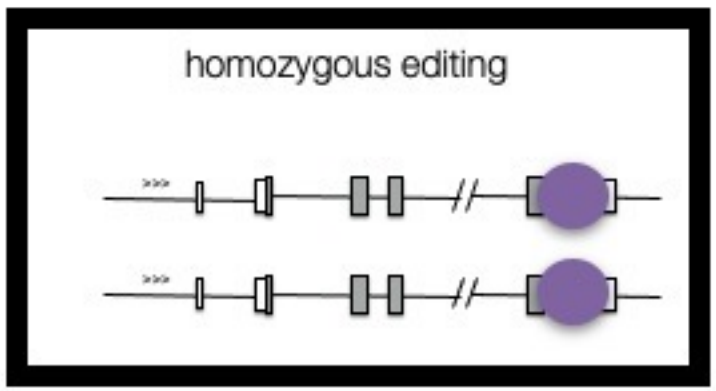
Prototypes:

CDELs = CDK1 and TOP2a

suicide gene = HSV-TK

bicistronic mRNA

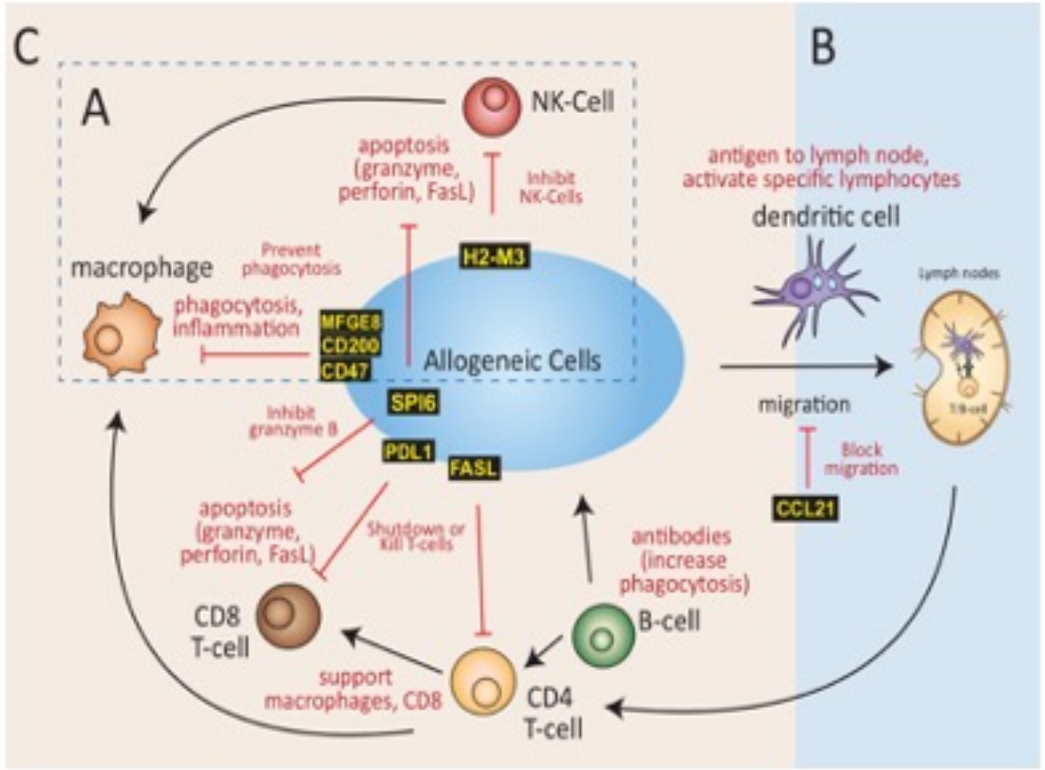




Nature. 2018 Nov; 563: 701-704

Our Patented Technologies- induced Allogeneic Cell Tolerance (iACT)

Transgenic overexpression of eight immune response modulating cell surface and local acting genes



Cloaking genes

1) Mitigating initiation of adaptive immunity by antigen presenting cells,
2) Blocking cytotoxic activity of T-cells and NK-cells, and their cytolytic components and
3) Modulating inflammatory and phagocytotic monocytes and macrophages

- Pd-L1
- CD200
- CD47
- H2-M3
- FasL
- Spi6
- Mfge8
- Ccl21

No HLA KO
Locally acting
Several other combinations possible

self defence
mitigate recognition as foreign

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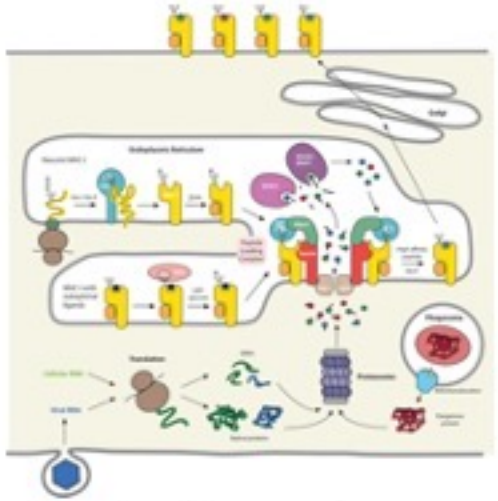
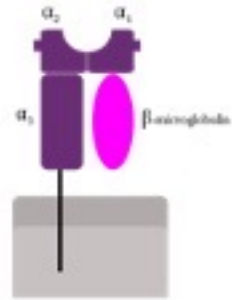
Our Patented Technologies- Hypoimmunogenic



- Complex of processing enzymes including Tapasin which regulate efficient processing
- Generally expressed on most cells
- Absence of self antigens leads to NK attack
- HLA E and G and F may regulate NK activity
- CD47, PDL1, CTL4 may inhibit immune response as well

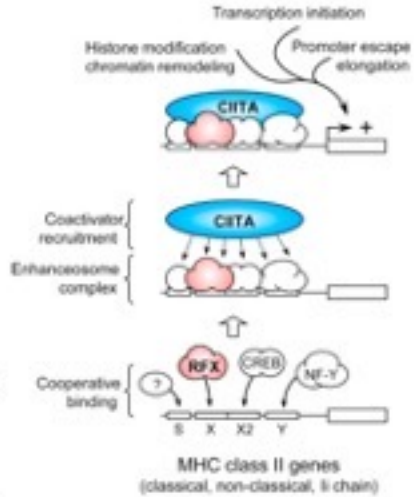


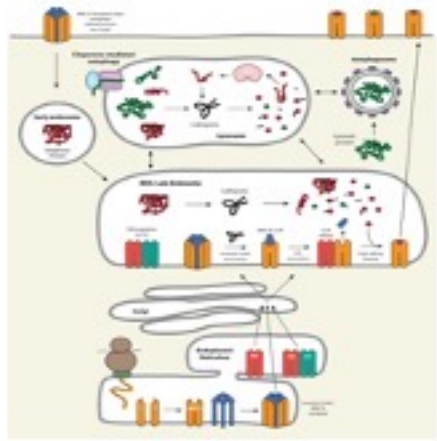
The MHC class I locus is complex and knocking out each group is difficult

Knocking out the invariant chain leads to loss of expression of all MHC Class I genes (including the possibly inhibitory genes) is much more reliable and has been done repeatedly with little effect on IPSC or differentiated cell function

B2M null mutations are known in humans and cause effects specific to the hematopoietic system

B2M and CTIIA null IPSC cells





- Generally present exogenous peptides

CTIIA mutations identified in BLS (bare lymphocyte syndrome) lead to loss of HC class II expression

CTIIA narrowly expressed in APC so KO should not have pleiotropic effects in contrast to RFANX and other factors that regulate Class II expression.

IPSC derived CTIIA null differentiated cells should not be able to present antigen even if the differentiated population contains AP capable cells

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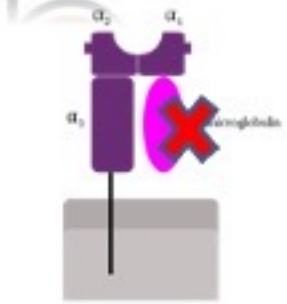
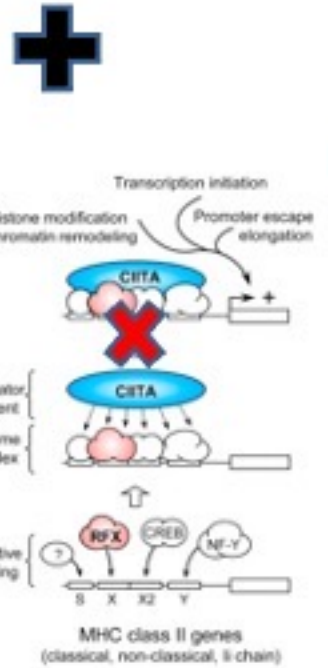
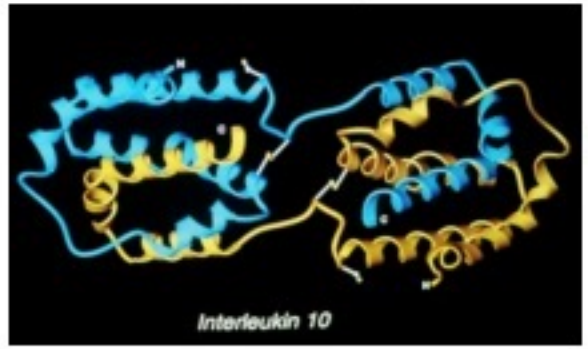
Our Patented Technologies-
Hypoimmunogenic

B2M and CTIIA null ++ IPSC cells



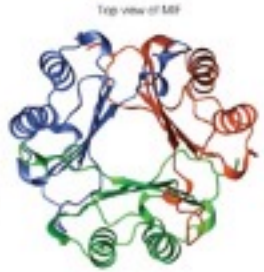


IL-10



AND/OR

MIF 1Alpha



Cells not recognized by adaptive immune system

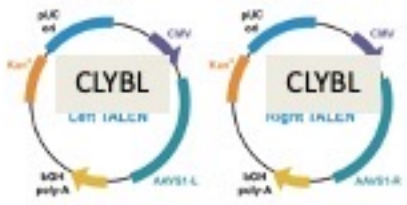
Innate immune system NK cells are inhibited via downregulation of NK activating receptors (NKG2D) and Macrophages migration Inhibited by MIF .

MIF enhances survival of cells via inhibiting apoptotic pathways

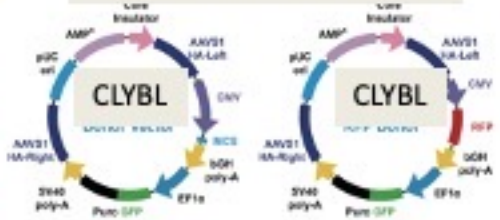
IL-10 is a master regulator and has multiple effects on T and B cells and converts them to a tolerogenic phenotype.
Regulates NK cell activation

Our Patented Technologies- Safe Harbor

CLYBL Editing vectors

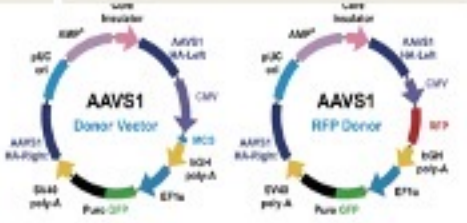


CLYBL Donor vectors



AAVS1 Editing vectors

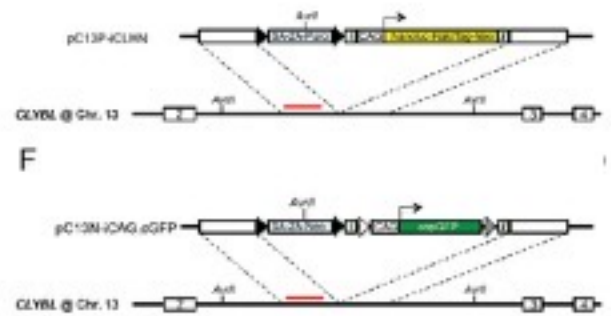
AAVS1 Donor vectors



Insert desired gene into a know well defined site where we have a patent
Use same constructs, same cell line to ensure consistent manufacturing and approval
Target both sites to express multiple products
Use insulators and strong promoters to ensure expression in differentiated cells

OR Make a master cell line and use CRE-LOX

Add Additional
Speed & Flexibility



FTO (Freedom To Operate)

- Make iPSC- NIH license
- Gene editing technology (knock-in and Knock out): Meganuclease, ZFN, Talen, CRISPR/cas9 and variants
- Gene insertion technologies (transposon technology): Sleeping beauty, Piggy bac and variants
- Conditional regulation of gene expression (In negotiation)
- Immortalization of cells: myc, TERT, EBNA, SV40-Large antigen etc
- Differentiation into specific cell types: Patents, knowhow, media and process and some licensed patents
- Fail safe , cloaking, hypoimmunogenic and safe harbor technologies to make second generation products
- RxCELL partnership and access to their patent portfolio

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RxCELL patents & FTO

- Methods and Compositions for Rapid Generation of Single and Multiplexed Reporters in Cells. WO/2016/099971. Issued US patent number: 10787644
- Hypoimmunogenic Cells and Uses Thereof in Immune Responses. Serial No. 63/025,351.
- Hypoimmunogenic Cells and Methods and Compositions for Their Production. Serial No. 63/005,651
- Method for Generating Multiple Cellular Products from Single Pluripotent Cell Source. Serial No. 62/641,570.
- Engineering Mesenchymal Stem Cells using Homologous Recombination. WO/2016/077273

Available Cell Lines

No	Technologies	Parent Line	Cell Line
1	Single Failsafe	NIH Line	PCA1 po #14
			TC-1133 CDK1 spCas9
			TC-1133 TOP2A spCas9
2	Double Failsafe	NIH Line	dFS #19
			dFS B23 po
			TC-1133 CDK1+TOP2A
3	Cloaked	NIH Line	PAN3 7F 3.13.7 Marker out
			PAN3 8F 1.1.1/1.1.3 marker out
4	Tinimas	NIH Line	PAN3 CDK1 Tinimas Clone 13
			PAN3 CDK1 Tinimas Clone 38
			PAN3 TOP2A Tinimas Clone A20
5	Inducible Immortalization	NIH Line	PAN3 Inducible Immortalization (Bulk)

Cell Lines continued

No	Technologies	Parent Line	Cell Line
6	Hypo-Immunogenic	NIH Line	RCL-BC IL10
			RCL-BC MIFa
			RCL-BC IL10 + MIFa Clones 2,3, 5
		SK005.3	SK5BC Clone C4 SK5BC Clone H2
			SK5BC + IL10
			SK5BC + MIFa
			SK5BC + IL10/MIFA
7	Unmodified	NIH Line	PAN3
			TC-1133
		SK005.3	SK005.3

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Thank you

Jake Krembil, COO

jake@pancella.com