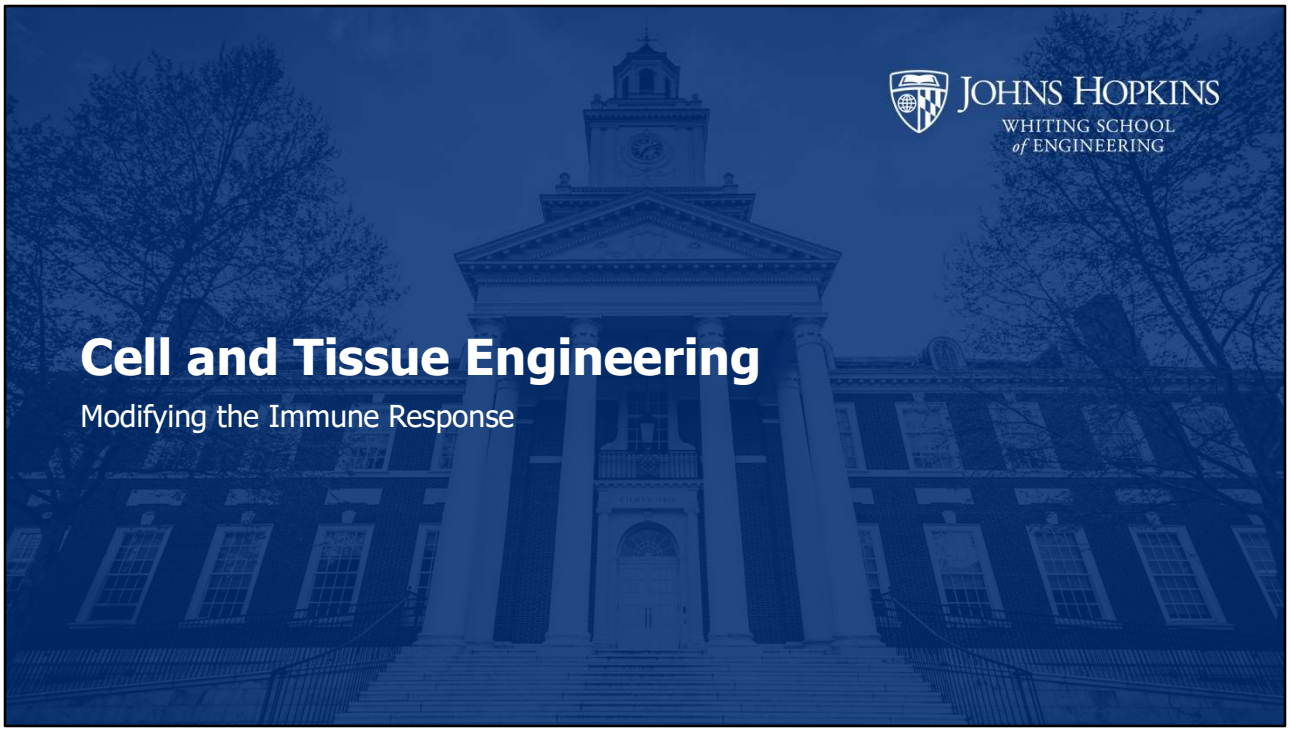

Cell and Tissue Engineering

Modifying the Immune Response

How Can We Modify the Immune Response?

Strategy	Description
Pharmacological treatment	
Tissue typing	
Genetic modifications	
Tolerance induction	
Spontaneous tolerance	
Physical immunoisolation	

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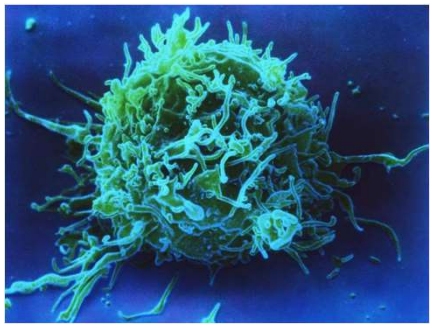
With the major risks and considerations mapped out we now have a good understanding of why cell and tissue engineered therapies almost certainly require modification of the immune response.

There are 6 major strategies used for such purposes and I've put them here for you in a table.

Immune Response Modification – Pharmacological

Strategy	Description
Pharmacological treatment	Immunosuppression (cyclosproine, FK506, rampamycin)
Tissue typing	
Genetic modifications	
Tolerance induction	
Spontaneous tolerance	
Physical immunoisolation	



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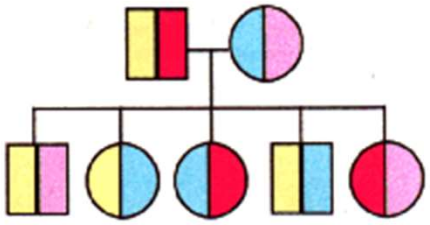
The first is pharmacological treatment – immunosuppression via prevention of T-cell activation.

Alternately you can block cytokine production downstream of T-cell activation using corticosteroids.

NEW – Interleukin blockers??

Immune Response Modification – Tissue Typing

Strategy	Description
Pharmacological treatment	Immunosuppression (cyclosproine, FK506, rampamycin)
Tissue typing	ABO antigens & HLAs
Genetic modifications	
Tolerance induction	
Spontaneous tolerance	
Physical immunoisolation	



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Tissue typing does not directly modify the immune response but instead can reduce the response.

This includes both blood type matching and HLA matching. You inherit a set of3 human leukocyte antigen's from each parent.

There are many HLA combinations, however it is still possible to match someone outside your family tree. Once a donor is found cross matching must also be done where serum from the donor is supplied to white blood cells from the recipient to make sure that the recipient has no antibodies to the donors cells.

When looking or a donor you don't want a positive cross match because this means the host cells will destroy the donors.

Immune Response Modification – Genetic Modification

Strategy	Description
Pharmacological treatment	Immunosuppression (cyclosproine, FK506, rampamycin)
Tissue typing	ABO antigens & HLAs
Genetic modifications	Humanizing xenograft
Tolerance induction	
Spontaneous tolerance	
Physical immunoisolation	

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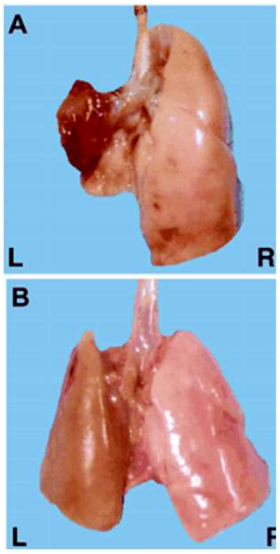
Genetic modification of a xenograft has involved expression of human enzymes which can participate in the complement cascade (of the immune system).

One such enzyme is fucosyl transferase

Immune Response Modification – Tolerance Induction

Strategy	Description
Pharmacological treatment	Immunosuppression (cyclosproine, FK506, rampamycin)
Tissue typing	ABO antigens & HLAs
Genetic modifications	Humanizing xenograft
Tolerance induction	Lowering the immune response without chronic treatment
Spontaneous tolerance	
Physical immunoisolation	



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Although it hasn't been fully achieved ample work is being done in the field of tolerance induction. These are ways to block the immune response without the need for chronic immunosuppression.

This is highly desirable because chronic immunosuppression leaves the patient without defenses. Research in this area includes work on blocking co-stimulators of T cell activation, which when blocked can turn an activation signal into a deactivation signal.

You can see the results of a left lung transplant here in a rat without and with tolerance induction strategies. Without it the left allograft is completely destroyed. With it the the transplanted lungs show mild acute rejection.

Immune Response Modification – Spontaneous Tolerance

Strategy	Description
Pharmacological treatment	Immunosuppression (cyclosproine, FK506, rampamycin)
Tissue typing	ABO antigens & HLAs
Genetic modifications	Humanizing xenograft
Tolerance induction	Lowering the immune response without chronic treatment
Spontaneous tolerance	After years of immunosuppression
Physical immunoisolation	

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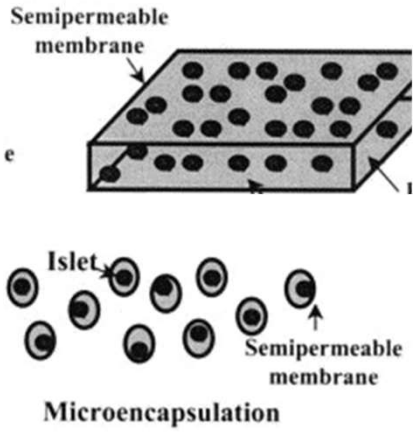
With no modification at all there have been cases of spontaneous tolerance.

These are patients who were taken off of chronic immunosuppression showed acceptance of the foreign tissue.

Last module we discussed how micro-chimerism may play a role in these mechanisms.

Immune Response Modification - Immunoisolation

Strategy	Description
Pharmacological treatment	Immunosuppression (cyclosproine, FK506, rampamycin)
Tissue typing	ABO antigens & HLAs
Genetic modifications	Humanizing xenograft
Tolerance induction	Lowering the immune response without chronic treatment
Spontaneous tolerance	After years of immunosuppression
Physical immunoisolation	Using semi-permeable barriers



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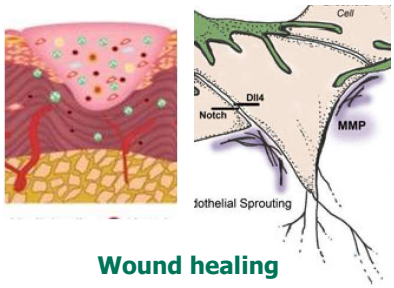
Last we have physical immunoisolation techniques which use barriers to keep the foreign material from the host.

These barriers allow molecular diffusion of cell-based products out and nutrient in while blocking trafficking of immune cell in.

On the right, I'm showing you both bead encapsulation and semipermeable membrane methods which are employed with transplanted pancreatic islet cells in efforts to cure diabetes.

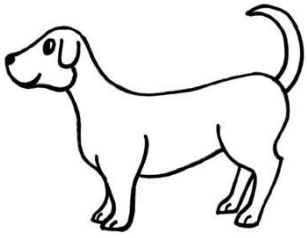
What Do We Know About Host Integration?



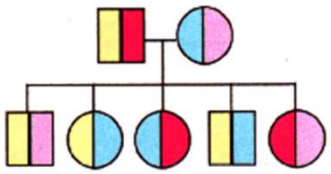
Wound healing

Angiogenesis

Immune response



Innate and Adaptive Immunity



Modulating the immune response in CTE

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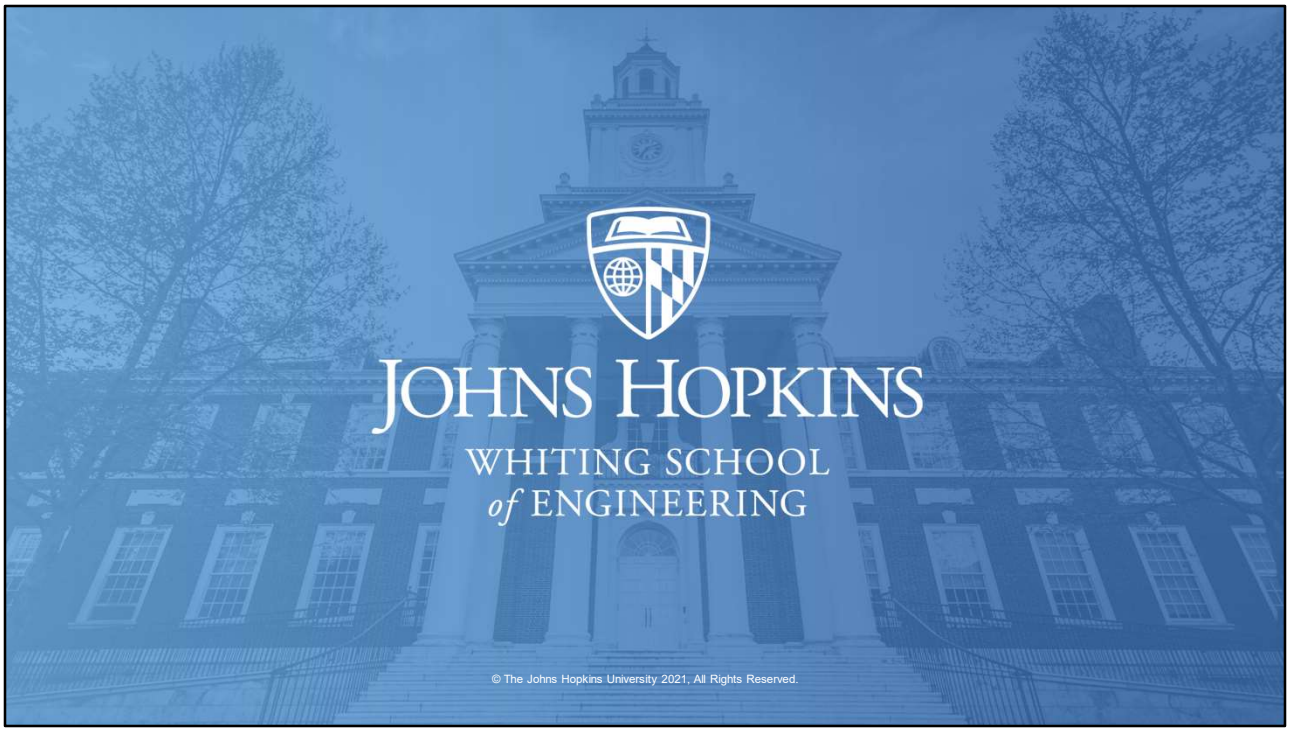
Marshall, JA 2012

We began be discussing the processes which will impact integration of cell and tissue engineered therapies. These included wound healing, angiogenesis and the immune response.

You likely want to slow wound healing, modulate angiogenesis depending on the target tissue, and decrease or tune the immune response.

We covered the basics of adaptive and innate immunity so that we could then discuss ways to work around the immune system when employing cell and tissue engineered strategies.

Next week we'll move forward in our journey from material to cell source in a module on stem cells. The various types, their advantages and their application to cell and tissue engineering.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