Johns Hopkins Engineering

# Immunoengineering

## Immunoengineering—Allergy and Autoimmunity

Tolerance Through Particles

JOHNS HOPKINS
WHITING SCHOOL
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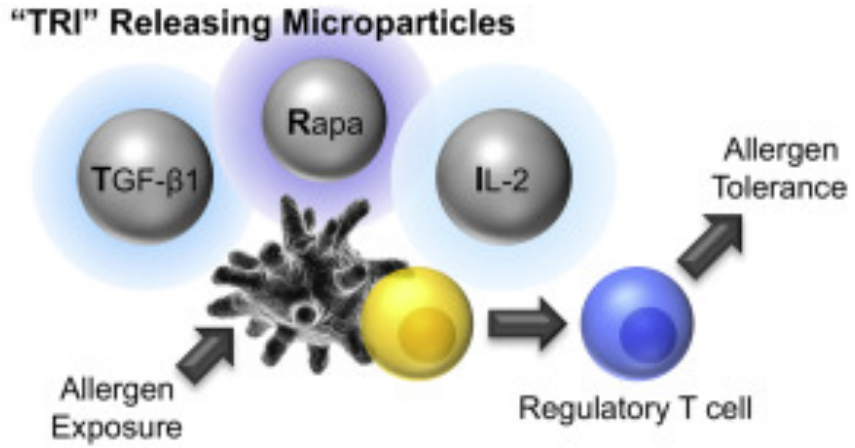
# Case Studies to Illustrate Design Principles

- Replicating tolerance at the cellular level - particles
- Replicating tolerance at the organ level - scaffolds
- Delivery of allergen immunotherapy

# Cytokine-particles induce Tregs for Allergies

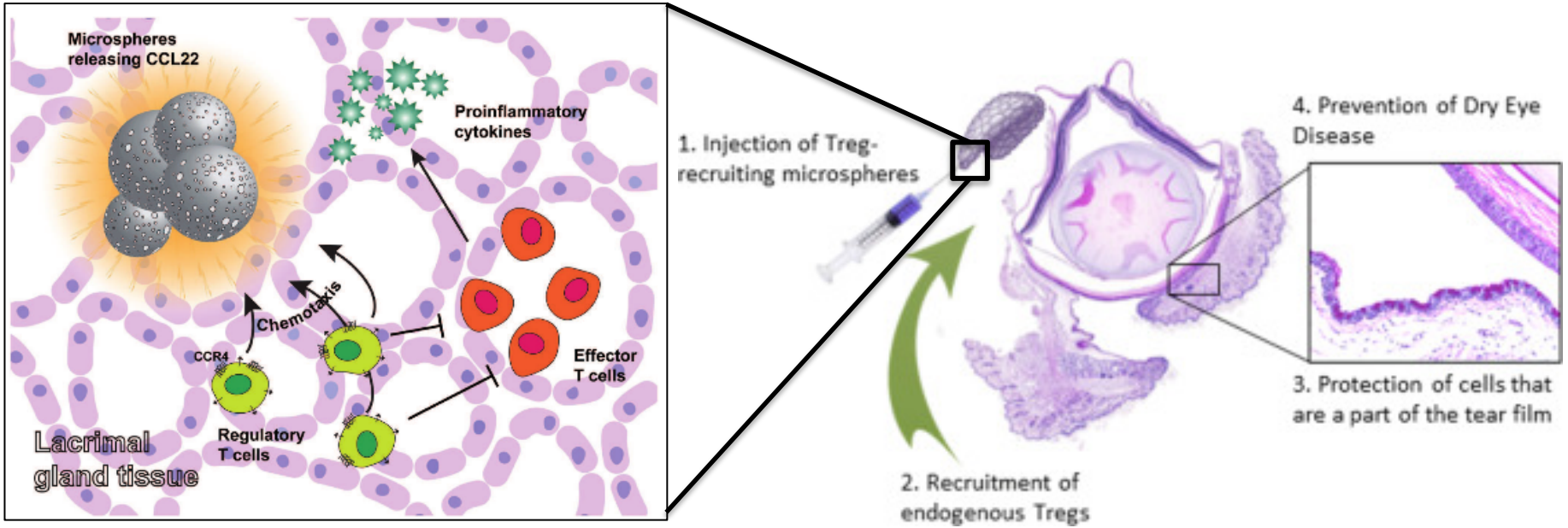
- IL-2 and TGF-b1 have short half-lives and off-target effects
- Microparticles allow for sustained release, local release, and dose sparing
- Soluble = Limit effector
- Particle = Induce Treg






Balmert, Stephen C., et al. "In vivo induction of regulatory T cells promotes allergen tolerance and suppresses allergic contact dermatitis." *Journal of Controlled Release* 261 (2017): 223-233.

# Chemokine Particles to Recruit Tregs (Dry Eye Disease)



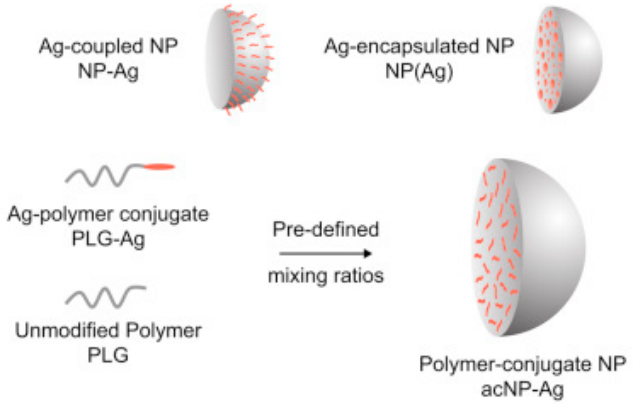

- Slow release to establish a long-term gradient



Ratay, Michelle L., et al. "Treg-recruiting microspheres prevent inflammation in a murine model of dry eye disease." *Journal of Controlled Release* 258 (2017): 208-217.
Ratay, Michelle L., et al. "Modern Therapeutic Approaches for Noninfectious Ocular Diseases Involving Inflammation." Advanced healthcare materials (2017).

# Nanoparticle Design for Treating Multiple Sclerosis

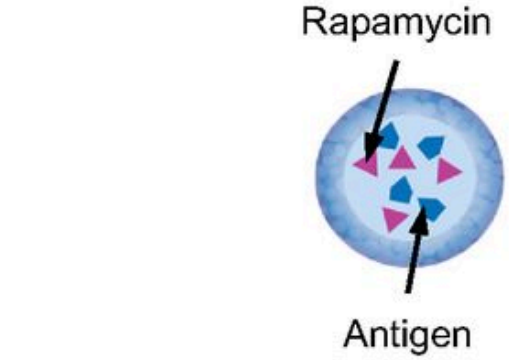
- Nanoparticle size can be used as carriers to target specific organs (lymph node targeting)
- 400 nm more effective than 80 nm
  - Want to facilitate uptake
- Directly conjugated antigen
  - Controlled antigen loading
  - Controlled size and zeta potential
  - Bind less IgG
- Control over properties, extended shelf-life, ease of manufacturing

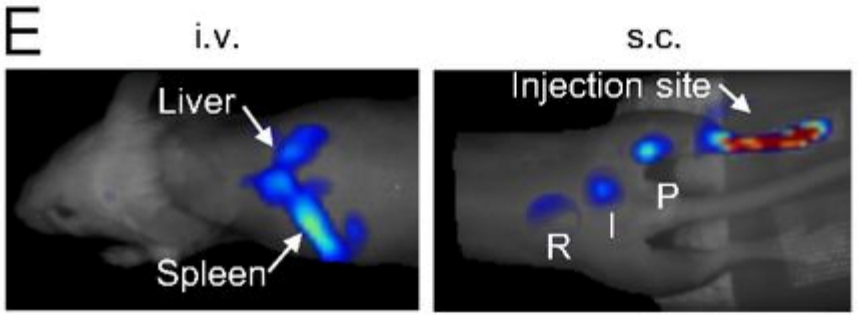



Pearson, Ryan M., et al. "Controlled delivery of single or multiple antigens in tolerogenic nanoparticles using peptide-polymer bioconjugates." *Molecular Therapy* 25.7 (2017): 1655-1664.

# Combining Antigen & Immunomodulation

- Combine antigen & rapamycin
  - Colocalization - Both need to be in same particle or immunogenic
- Take advantage that most particles end up in the spleen
- Control over multiple challenges with pro-inflammatory signals



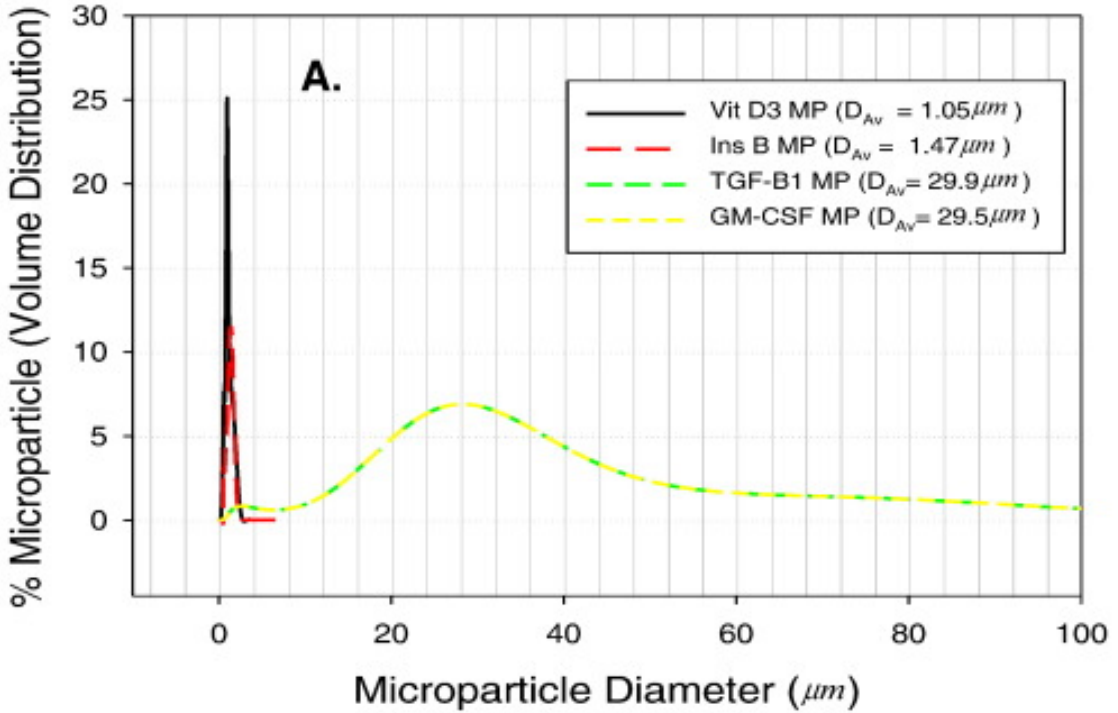






Maldonado, Roberto A., et al. "Polymeric synthetic nanoparticles for the induction of antigen-specific immunological tolerance." *Proceedings of the National Academy of Sciences* 112.2 (2015): E156-E165.

# Tolerogenic Microparticles Prevent Type 1 Diabetes

- 2 particle sizes to control uptake
  - Ins. & Vit D3 in small microparticle
  - TGF-b1 & GM-CSF in large microparticle
- Recruit, polarize, and tolerize for T1D prevention

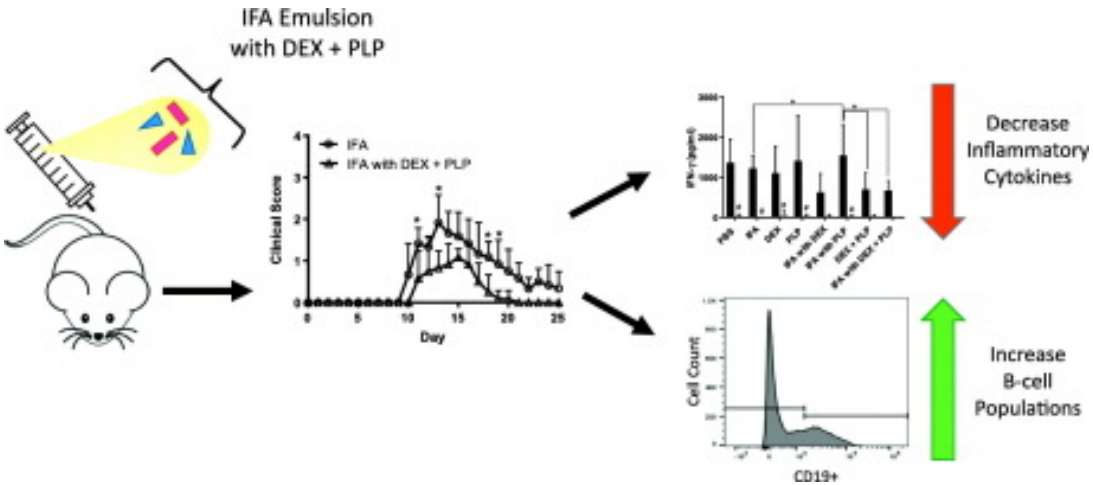





Lewis, Jamal S., et al. "A combination dual-sized microparticle system modulates dendritic cells and prevents type 1 diabetes in prediabetic NOD mice." *Clinical Immunology* 160.1 (2015): 90-102.

# Emulsion Based Injections

- Incomplete Freud's adjuvant form emulsion
  - parrafin oil and mannide monooleate
- Combination with Dexamethasone for sustained release of antigen

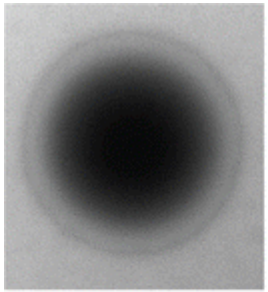


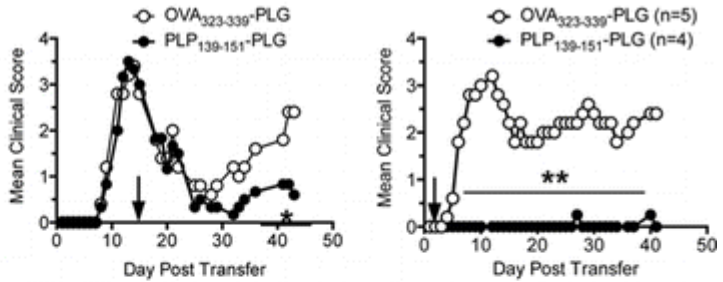


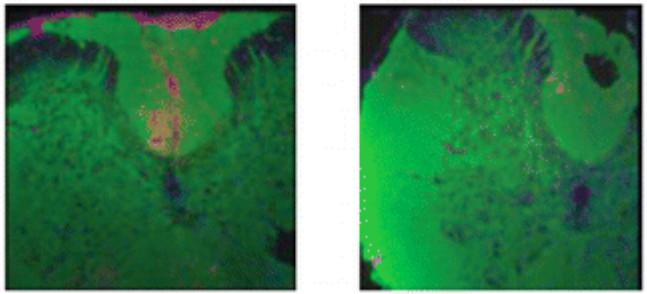

Northrup, Laura, et al. "co-delivery of autoantigen and dexamethasone in incomplete Freund's adjuvant ameliorates experimental autoimmune encephalomyelitis." *Journal of Controlled Release* 266 (2017): 156-165.

# Particles Compared to Cell-based Therapies

- Conjugate to surface of degradable particle
- 500 nm to mimic apoptotic fragments and enhance uptake in spleen
- High level of peptide conjugation required for Treg induction





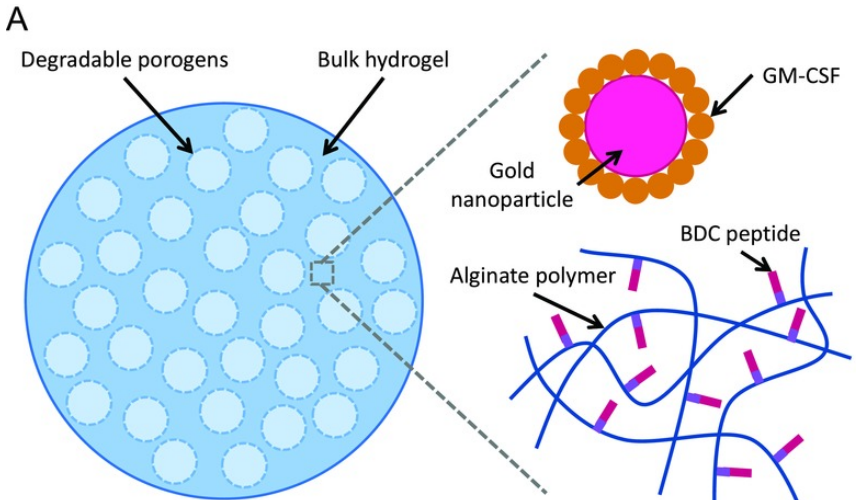
$OVA_{323-339}$-PLG $PLP_{139-51}$-PLG



Hunter, Zoe, et al. "A biodegradable nanoparticle platform for the induction of antigen-specific immune tolerance for treatment of autoimmune disease." *ACS nano* 8.3 (2014): 2148-2160.

# Can do with hydrogels as well

- Encapsulation in hydrogel
- Allows infiltration of cells to control regulatory environment

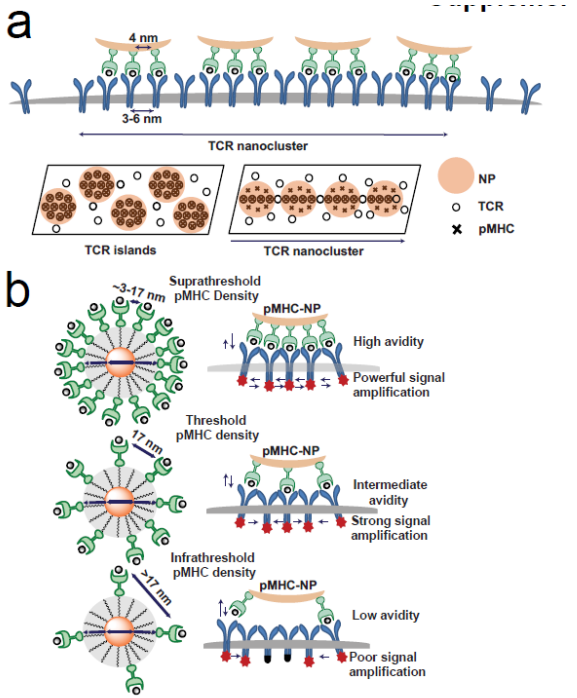





Verbeke, Catia S., et al. "Multicomponent Injectable Hydrogels for Antigen-Specific Tolerogenic Immune Modulation." *Advanced healthcare materials* 6.6 (2017).

# Bypassing APCs with artificial nanoparticle APCs

- Create aAPCs by attaching peptide-loaded MHC on the surface of Nanoparticles
- Without co-stimulatory signal this leads to tolerance
- High density of signal is needed to induce tolerogenic signals through TCR

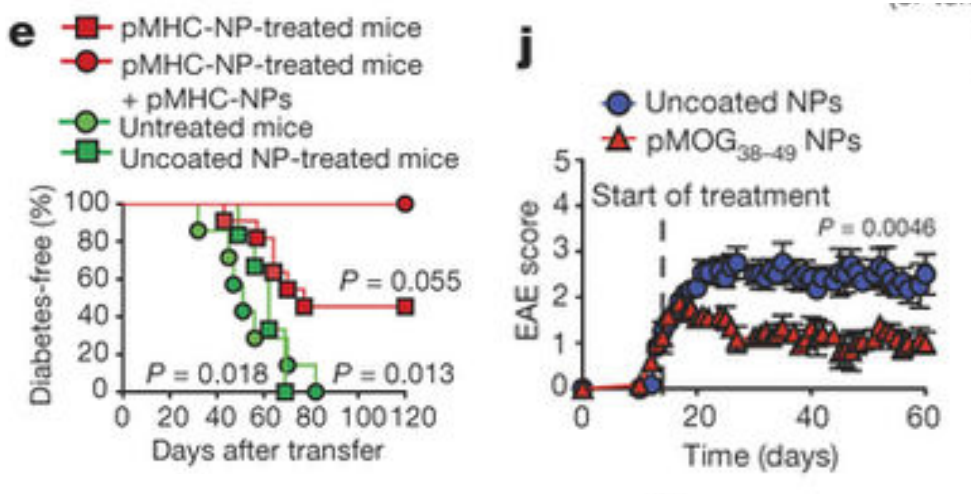





Singha, Santiswarup, et al. "Peptide–MHC-based nanomedicines for autoimmunity function as T-cell receptor microclustering devices." *Nature nanotechnology* 12.7 (2017): 701.

# Inducing Tolerance with Antigen-Presenting Cell Mimicking Particles

- Antigen-specific therapy
  - Requires knowledge of peptide
- Works in both mouse models of Diabetes and MS
- Induce regulatory-like antigen-specific CD8+ T cells






Singha, Santiswarup, et al. "Peptide–MHC-based nanomedicines for autoimmunity function as T-cell receptor microclustering devices." *Nature nanotechnology* 12.7 (2017): 701.

# Summary

- Particles allow spatial and temporal control over release of autoantigen and immunomodulatory factors
  - This leads to local induction of tolerance instead of systemic effects
- Particles may provide more cost-effective therapies when compared to biologic and cellular therapies
  - Shelf-life, scalability, standardization, manufacturing, availability
- Important considerations for particle therapy design
  - Administration route
  - Size
  - Shape
  - Surface charge
  - Antigen/chemokine loading technique
  - Material