



Nanoparticle Vaccine Carriers and Adjuvants:
Advancing a new nanotechnology platform from concept to clinic

Liquidia Technologies

4th Vaccine Renaissance Conference
22 October 2010

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Overview

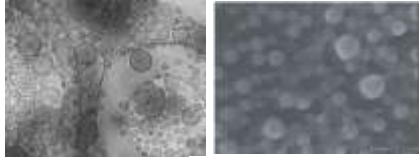
- Technology Introduction
- Platform Capabilities
- Vaccines Program
 - » Protein Vaccines & Lead Program
 - » Polysaccharide Vaccines

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Particle Approaches to Product Development

Old Paradigm: Bottom-Up Fabrication

- Use naturally existing small particles or harsh micronization techniques:



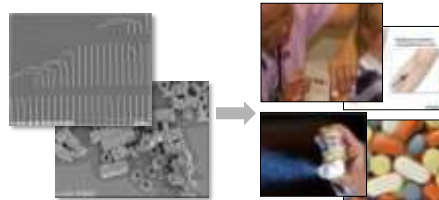
Liposomes
BIND Biosciences
Farokhzad et. al PNAS 2006, 103, 6315

- Polydisperse; difficult to scale
- Limited design options
- Variables highly interdependent
- Few successes; Doxil, Abraxane

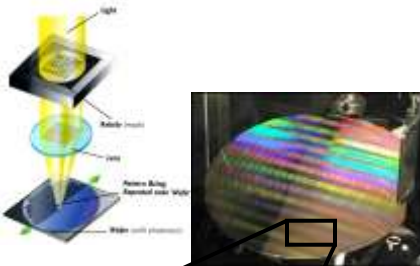
The PRINT® Paradigm: Top-Down Fabrication

- Engineer unique particles for specific needs:

- True monodispersity
- Control over key design parameters
- Tune variables independently
- Straightforward path to mfg scale



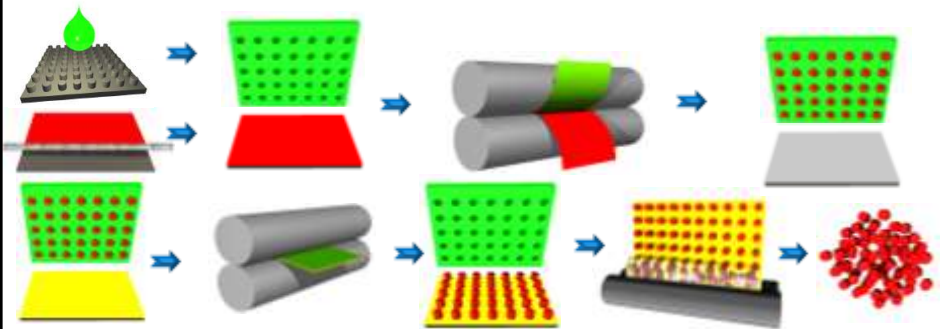
Micro- and Nano-fabrication in the Semiconductor Industry



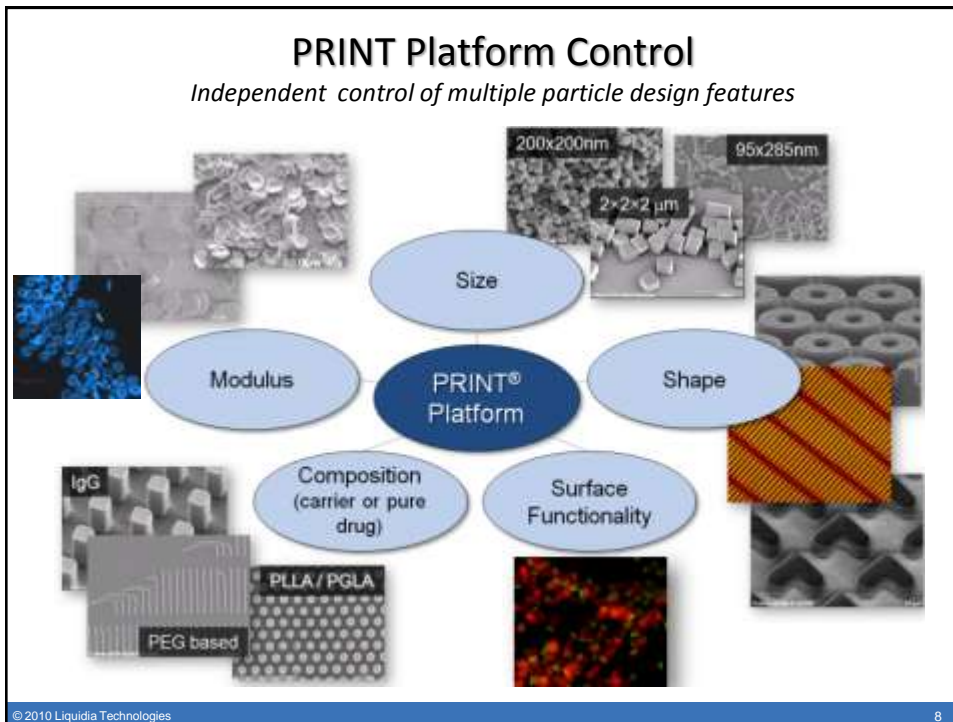
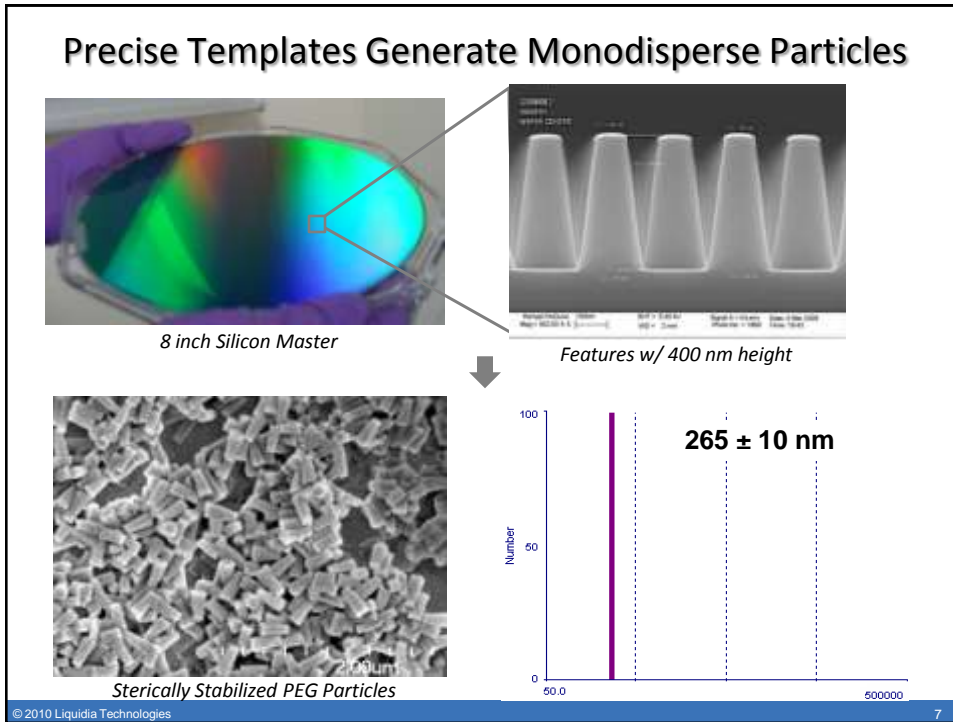
Year	Processor	Number of Transistors	Minimum Feature Size
1971	4004	2,300	10 micron
1972	8008	3,500	10 micron
1974	8080	6,000	6 micron
1978	8086	29,000	3 micron
1982	80286	134,000	1.5 micron
1985	80386	275,000	1.5 micron
1989	Intel 486	1.2 million	1.0 micron
1993	Pentium	3.1 million	800 nm
1997	Pentium II	7.5 million	350 nm
1999 (Feb)	Pentium III	9.5 million	250 nm
1999 (Oct)	Pentium III	28 million	180 nm
2000	Pentium IV	42 million	130 nm
2004	Itanium 2	592 million	90 nm
2007	Dual-Core Xeon	1.3 billion	65 nm
2010	8-Core Xeon Nehalem-EX	2.3 billion	45 nm

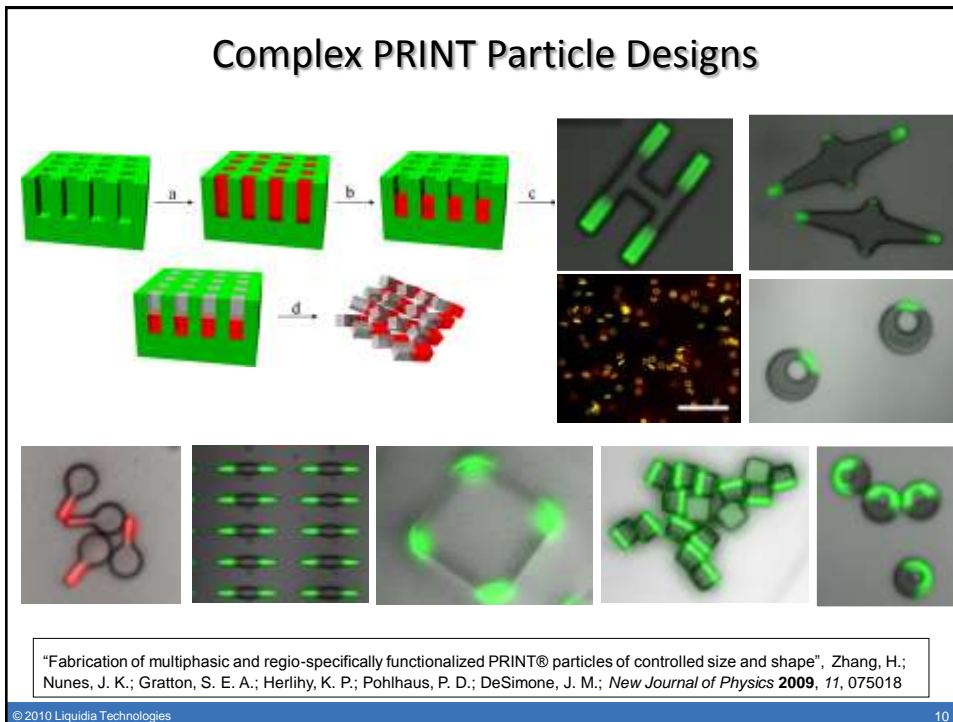
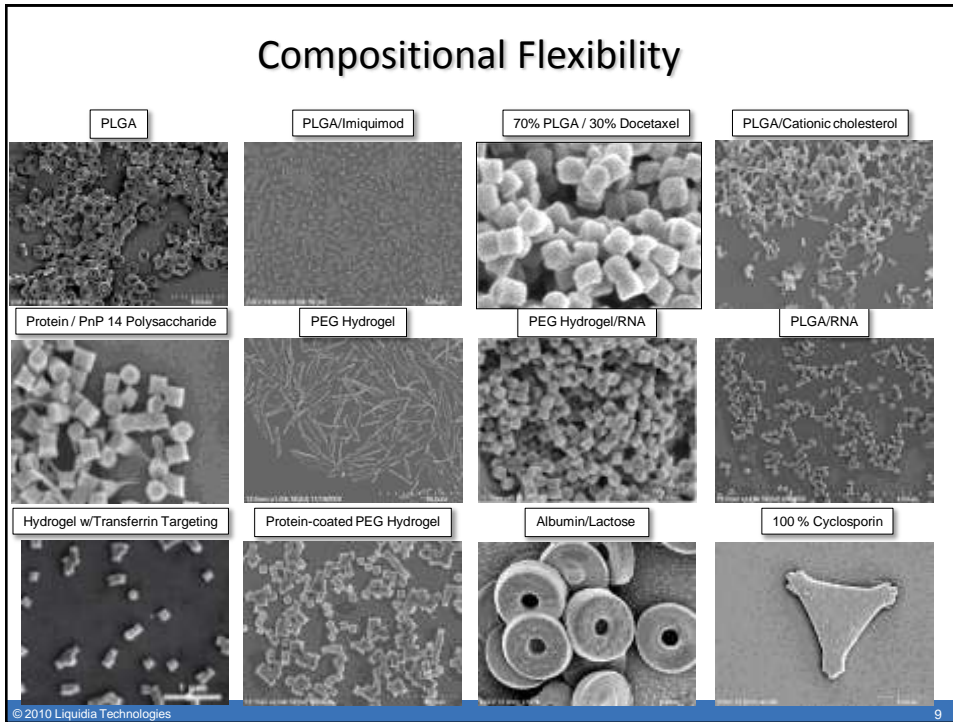
PRINT Platform Technology

Particle Replication in Non-wetting Templates (PRINT® Platform)



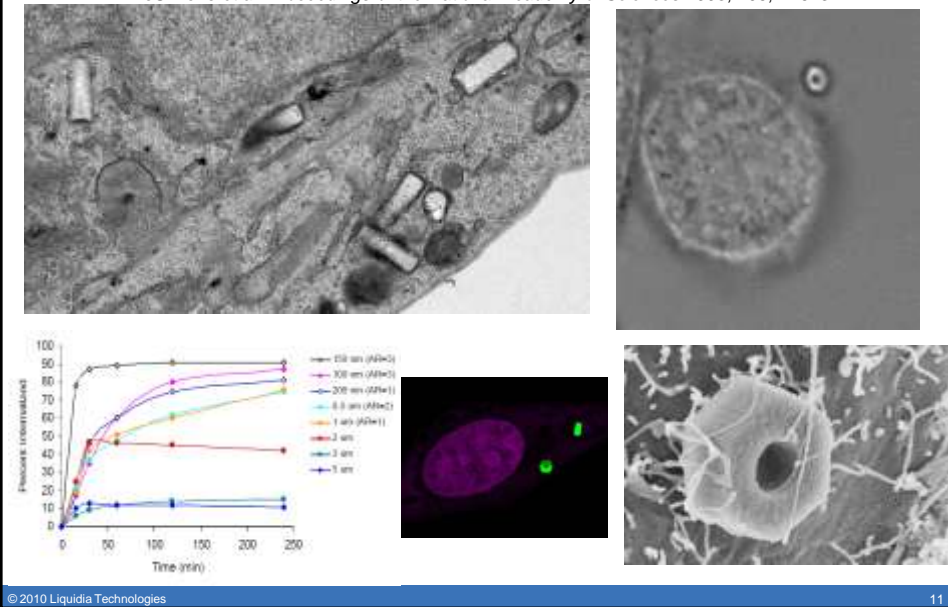
"Direct Fabrication and Harvesting of Monodisperse, Shape Specific Nano-Biomaterials"; Rolland, J. P.; Maynor, B. W.; Euliss, L. E.; Exner, A. E.; Denison, G. M.; DeSimone, J. M *J. Am. Chem. Soc.* **2005**, 127, 10096





Particle Size and Shape Influence Particle Cellular Internalization

DeSimone *et al.* *Proceedings of the National Academy of Sciences* **2008**, 105, 11613

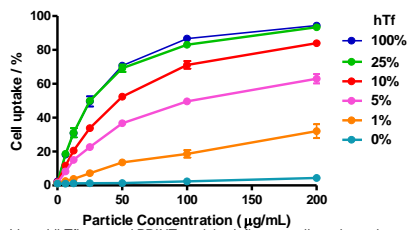


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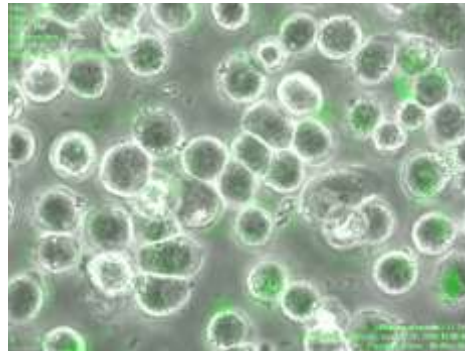
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Chemical Tunability Enables Unique Targeting, Loading and Release Options

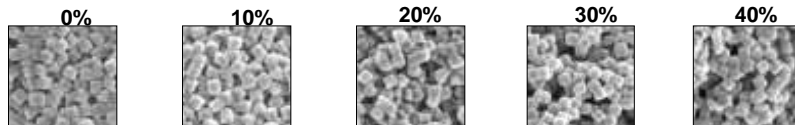
Precisely tune density of targeting ligands to enhance target selectivity



Ligand (hTf) targeted PRINT particles influence cell uptake and viability in Ramos cells



Size, Shape and Charge are Independent of Docetaxel Loading



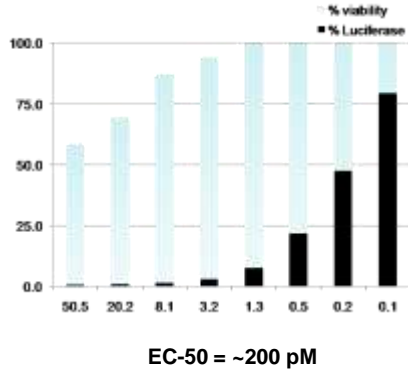
"Reductively Labile PRINT Nanoparticles for the Delivery of Doxorubicin to HeLa Cells"; Petros, R. A.; Ropp, P. A.; DeSimone, J. M.; *J. Am. Chem. Soc.* **2008**, 130, 5008-5009

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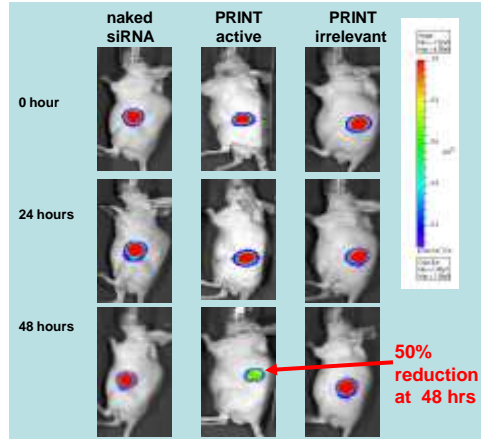
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In vitro and In vivo siRNA Delivery

In vitro Anti-Luciferase Model

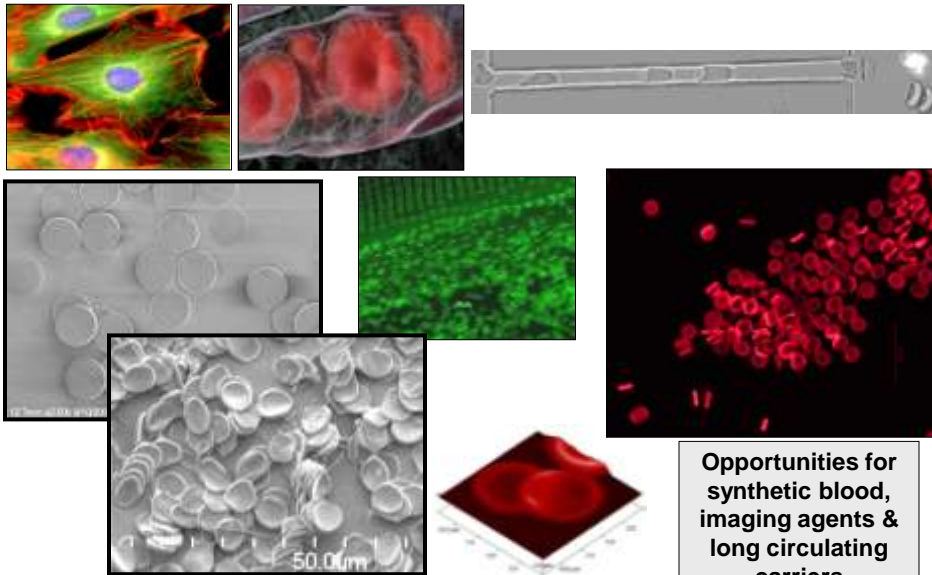


In Vivo PC-3 Xenograft Tumor Model

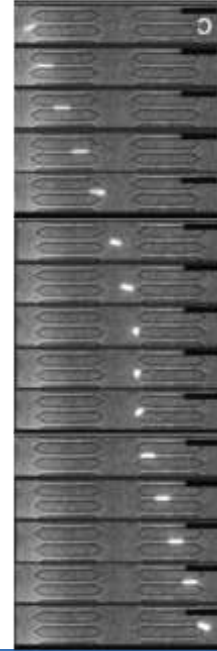
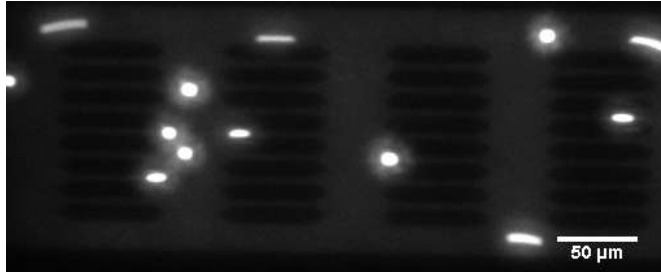


Role of Mechano-biology in Biodistribution:

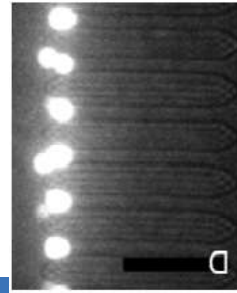
Inspired by Red Blood Cells and Metastatic Cancer Cells



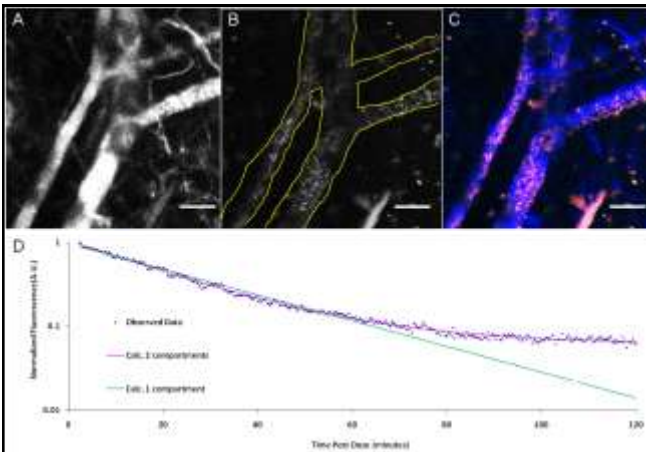
Mimicking Red Blood Cells



Component	Structure	Weight %
PEG ₄₀₀ diacrylate (PEGDA)	<chem>C=CC(=O)OCC(OCC)OC(=O)C=C</chem>	1-10
2-Hydroxyethylacrylate (HEA)	<chem>C=CC(=O)OCCO</chem>	78-87
Carboxyethyl acrylate (CEA)	<chem>C=CC(=O)OCC(=O)O</chem>	10
HCPK	<chem>C1=CC=C(C=C1)C(=O)C2(O)CCCC2</chem>	1
Polymerizable Fluorescent Dyes		1



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Modulus Control – Impact on Circulation Time

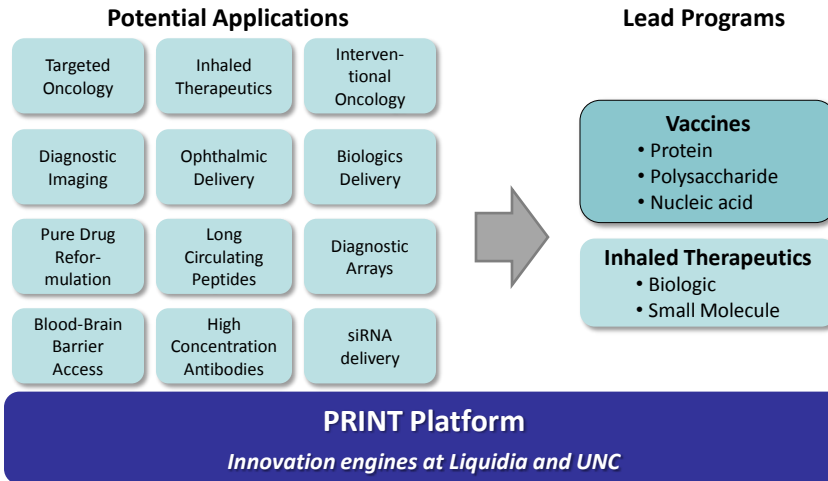
Blood draw out to 5 days post injection.

Full pk analysis from 2 compartment model

5% of the injected dose remaining in the blood after 5 days

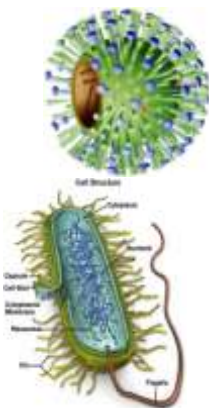
% Crosslinker	Modulus of Bulk Material (kPa)	Distribution Half-life (hours)	Elimination Half-life (hours)
10%	63.9 ± 15.7	0.038 ± 0.0012	2.88 ± 0.92
5%	39.6 ± 10.4	0.066 ± 0.036	5.12 ± 2.17
2%	16.9 ± 1.7	0.15 ± 0.025	7.12 ± 0.82
1%	7.8 ± 1.0	0.35 ± 0.13	93.29 ± 31.09

PRINT Technology Offers Broad Opportunities with Initial Focus in Vaccines



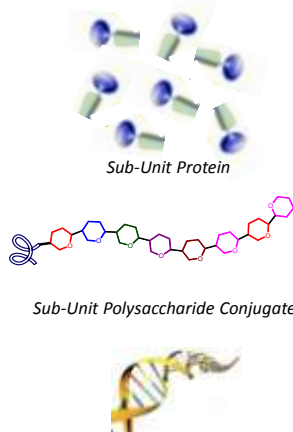
Vaccines Evolution

Whole Pathogens



- Highly efficacious
- Safety concerns

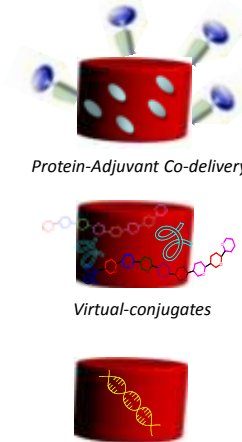
Sub-Unit and Nucleic Acids



Nucleic Acids: Vectedored or Naked

- Safer- but still safety concerns
- Efficacy and mfg. limitations

PRINT Vaccines



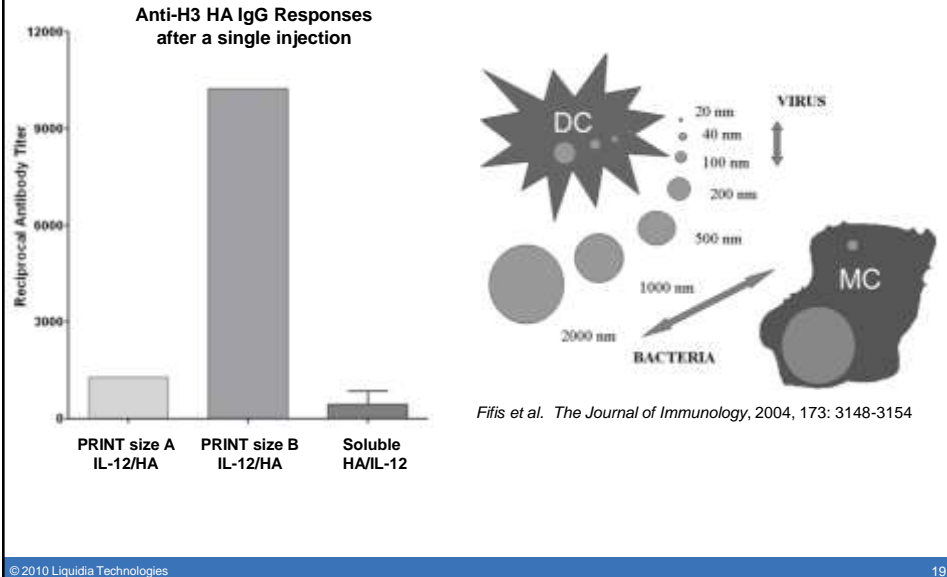
Protein-Adjuvant Co-delivery

Virtual-conjugates

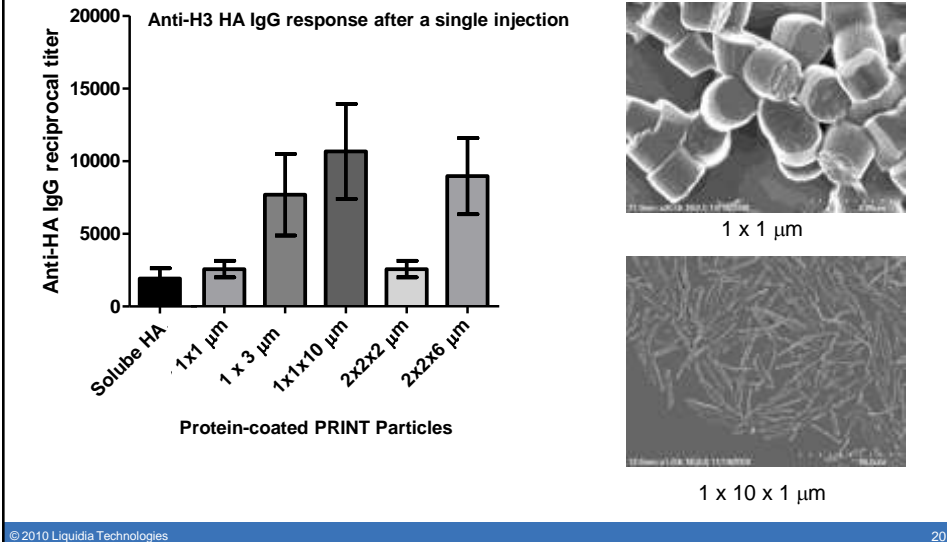
Synthetic Delivery System

- Optimized efficacy & safety
- Mfg. advantages

Particle Size Impacts the Immunogenicity of Adjuvant Co-delivery



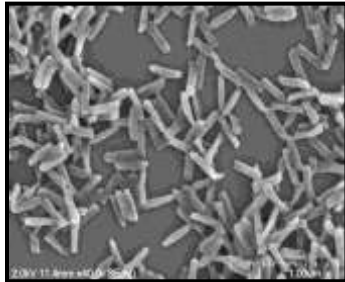
Influence of Size and Shape on Vaccine Immune Responses



Liquidia Product LIQ-001

Product Target

- Bio-absorbable nanoparticle carriers
- Enhance immune response in elderly
- Potential dose sparing in healthy young adults



Product Design

- 80 x 320 nm; sterile filtered
- Polymer-based with cationic additive
- Lyophilized

Key Attributes

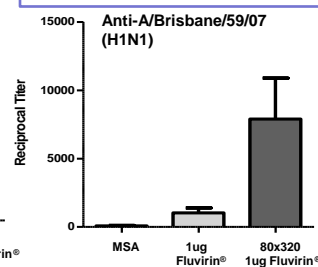
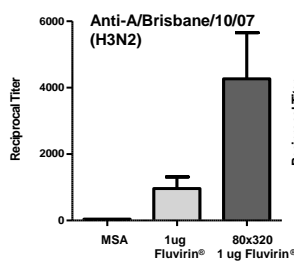
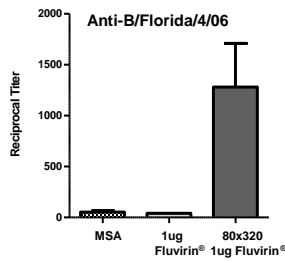
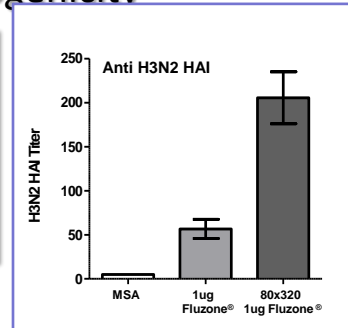
- Monodisperse
- Components with prior human use
- Focus on particle delivery; no adjuvant added
- Rapid binding of influenza proteins to particles
- Good safety profile in animals
- Can design to bind wide array of antigens

18 months Concept to Clinic

LIQ-001 – Preclinical Results Demonstrate Enhanced Immunogenicity



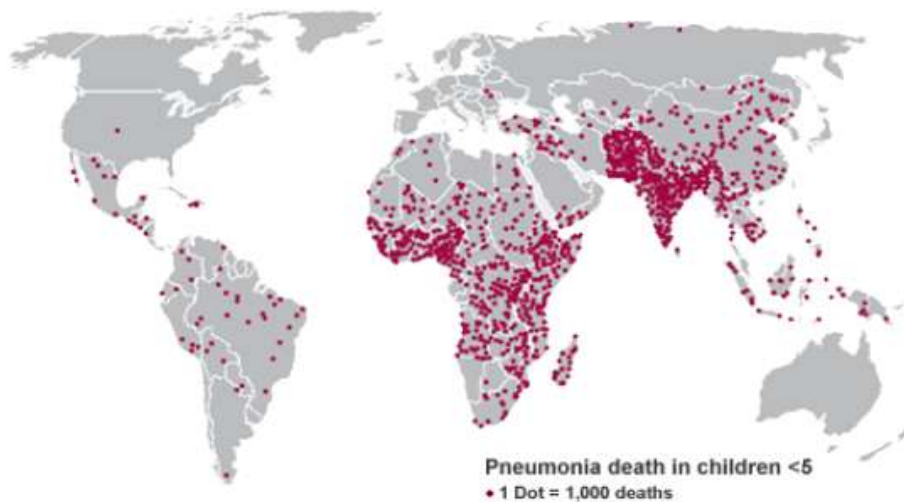
Lyophilized PRINT particles reconstituted with Influenza vaccine prior to injection



Polysaccharide Vaccine Program

Pneumonia is the leading cause of childhood mortality in the developing world

Nearly 70% of ~2 million child pneumonia deaths occur in Africa & So. Asia

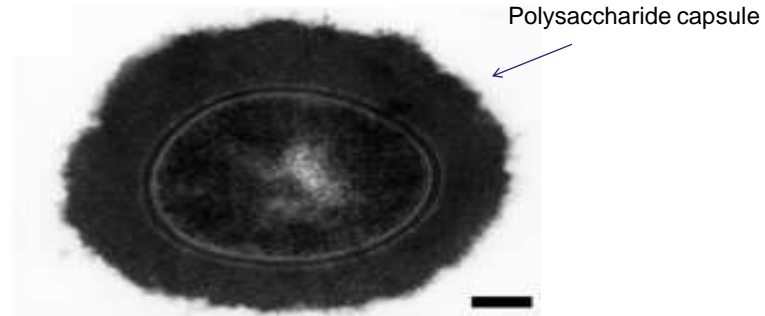


Source: World Bank

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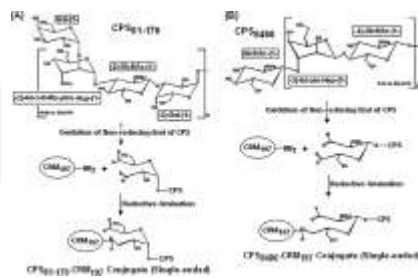
Streptococcus pneumoniae: leading cause of bacterial pneumonia



Hammerschmidt et al, Infection and Immunity, August 2005, p. 4653-4667, Vol. 73, No. 8, <http://iai.asm.org/cgi/content/full/73/8/4653>

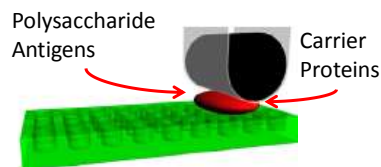
Liquidia's Approach to "Conjugates" Vaccines

Organic Chemistry Approach

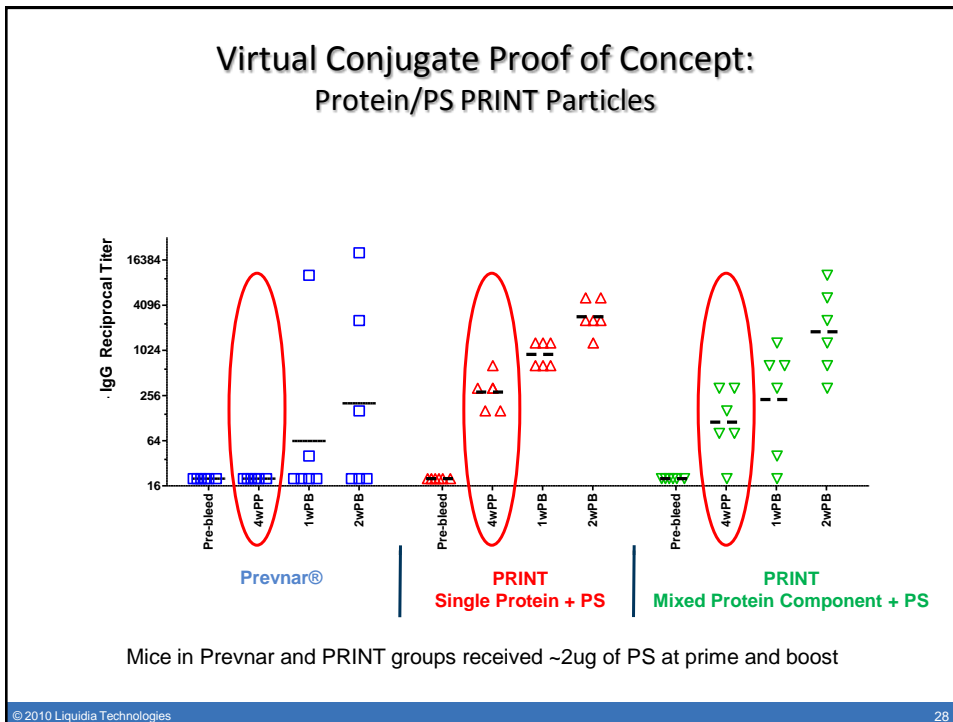
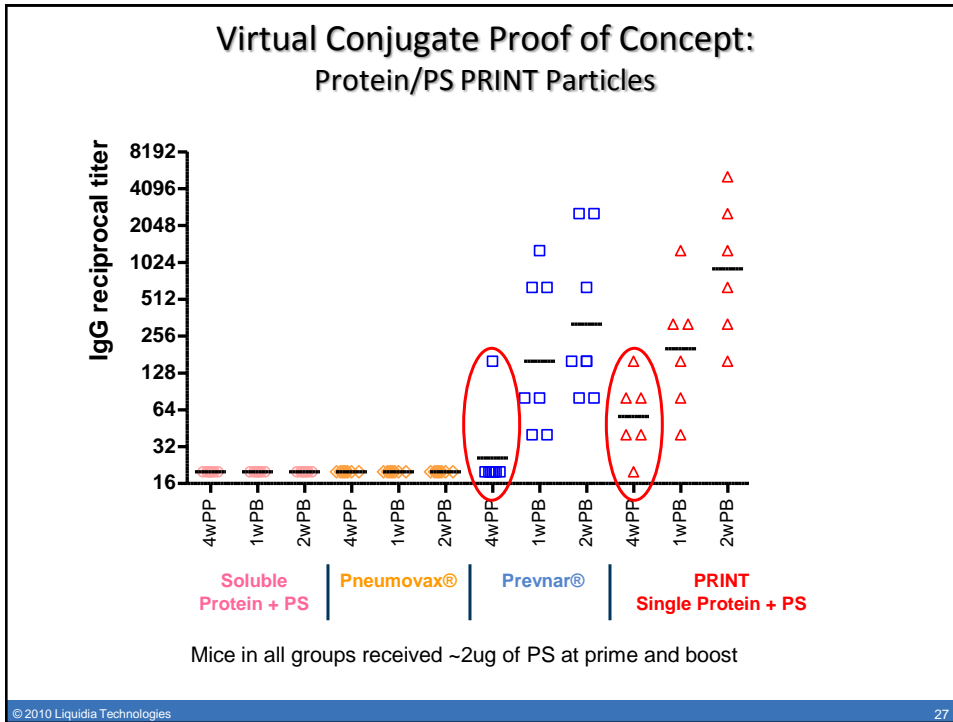


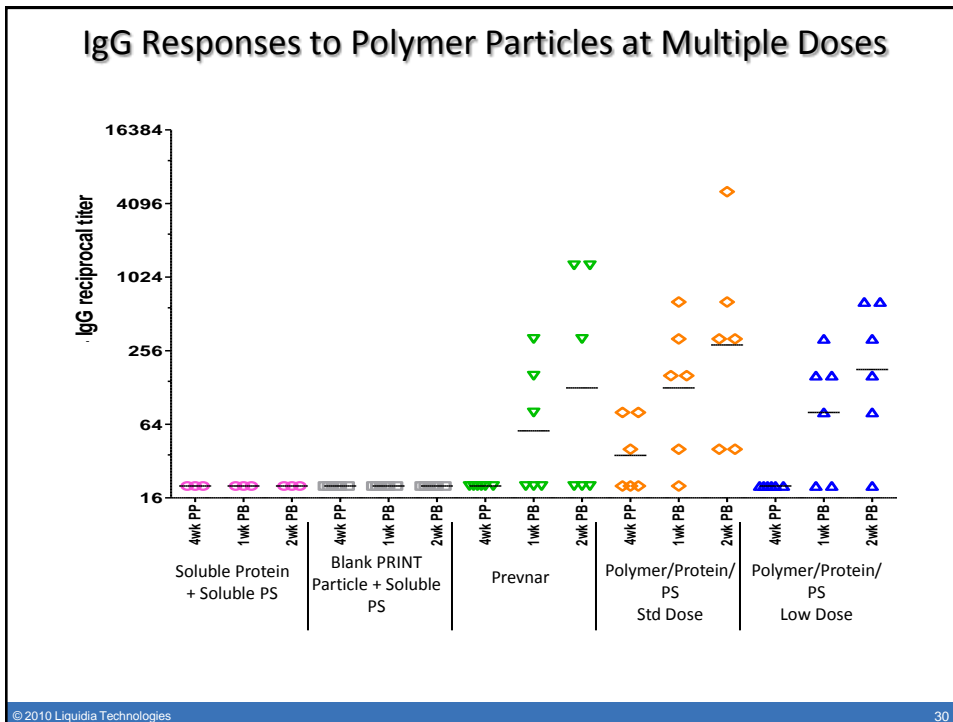
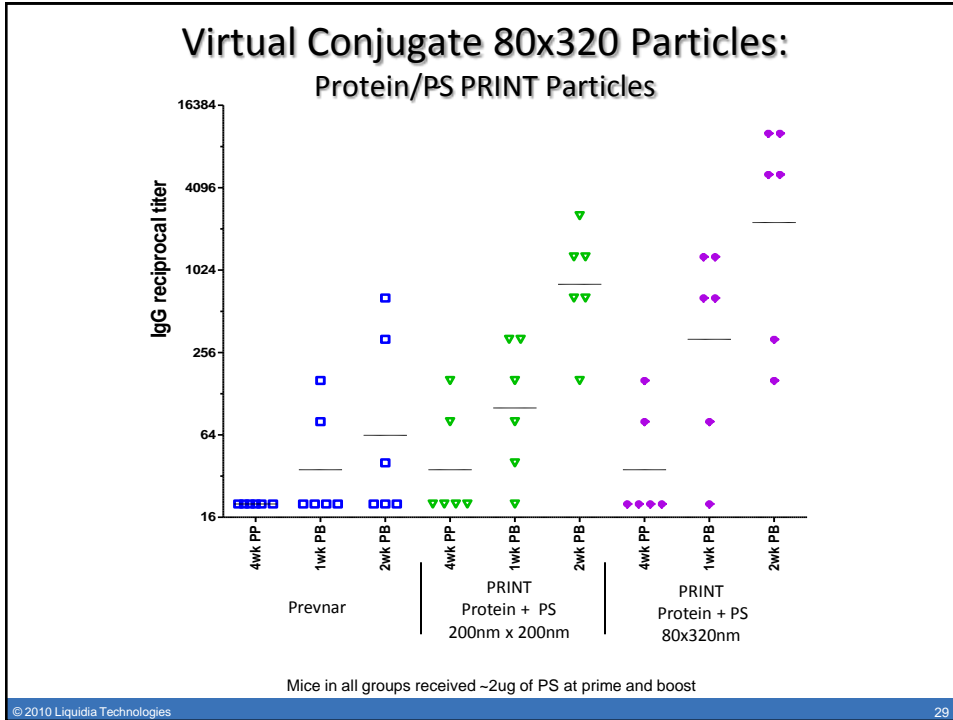
- Complex, low yield process
- Variable outputs

Engineering Approach Through PRINT



- Simple manufacturing
- Highly reproducible
- Self-adjuvanting particle





Status of Polysaccharide Vaccine Program

- Disruptive Cost and Scale
 - » Molding without complex chemistry
 - » Simplified, scalable manufacturing
 - » Rolls provide stable intermediate for storage/transport for fill/finish
- Technical Proof of Concept in Preclinical Studies
- Next Steps in Advancing Toward Clinical Development
 - » Evaluation of carrier protein options
 - » Design of multi-component vaccine

Management and Board of Directors

Management Team

Neal Fowler
Chief Executive Officer



Frank Malinoski, M.D., Ph.D.
Chief Medical Officer



Jonathan Smith, Ph.D.
Chief Scientific Officer



Bruce Boucher
Chief Financial Officer



Tom Templeman, Ph.D.
SVP, Integrated Supply Chain



Kyle Chenet
VP, Corporate Development



Board of Directors

Seth Rudnick, M.D. (Chairman)
Partner, Canaan Partners

Neal Fowler (CEO)

Stephen Bloch, M.D.
General Partner, Canaan Partners

Isaac Cheng, M.D.
Morningside Technology Advisory LLC

Joseph DeSimone, Ph.D.
Liquidia Founder, Distinguished Professor, UNC

Ed Mathers
Partner, New Enterprise Associates

Ralph Snyderman, M.D.
Chancellor Emeritus, Duke University,
James B Duke Professor of Medicine Emeritus

Acknowledgements



Influenza Vaccine Team Ashley Galloway, PhD, Project Lead

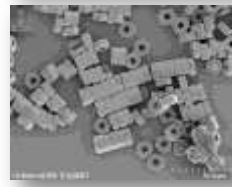
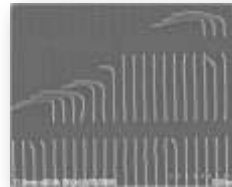
Joel Cohen	David Jensen	Casey Shanley
Jinny Conley	Jeff Kindig	Robin Spivey
Jie Di	Joe Marchand	Daria Stoltz
Jeremy Hansen	Sean Meng	Jun Tian
Chris Hinson	Andy Murphy	Jennifer White
Michael Hunter	Jen Procopi	

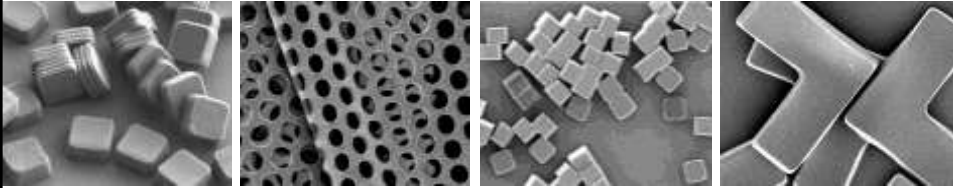
Virtual Conjugate Team Shyam Rele, PhD, Project Lead

Anton Beletskii	RiLee Robeson
Joel Cohen	Megan Rumley
Jie Di	Robin Spivey
Sean Gant	Jun Tian
Jeremy Hansen	Ying Zhang
Michael Hunter	

Summary

- Paradigm-shifting technology
 - » Nano-scale control of key design parameters
 - » Demonstrated manufacturing scale
 - » Distinct and defensible platform IP portfolio
- Broad platform opportunities
 - » Robust data emerging in vaccines
 - » Inhaled and siRNA programs demonstrating the benefit of shape and uniquely enabled chemistries
 - » Multiple additional partner-driven research programs
- First product entered clinical development in Fall of 2010
- Robust internal and partnership pipeline





Thank You

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