Spatio-Temporal Drug Delivery: Addressing the Unmet Medical Need

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Drug Delivery & Formulation, Berlin
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The opinions in this presentation are of the presenter and NOT of MSD

Public

Outline

- *Disease Area Trends and Unmet Medical Needs*

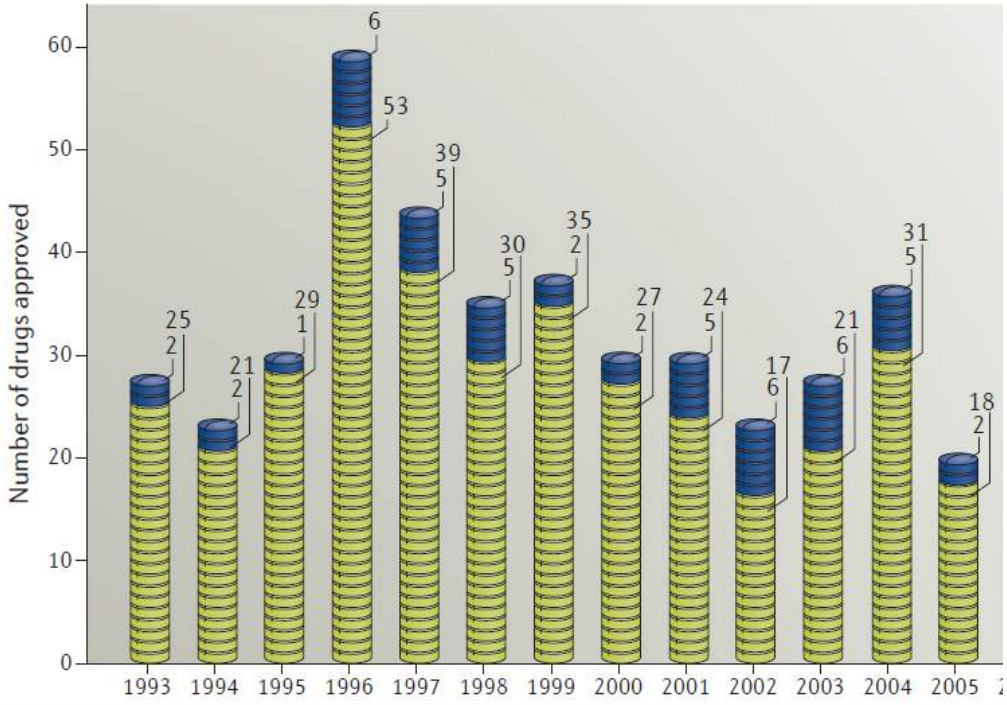
- *Role of Spatio-Temporal Delivery*

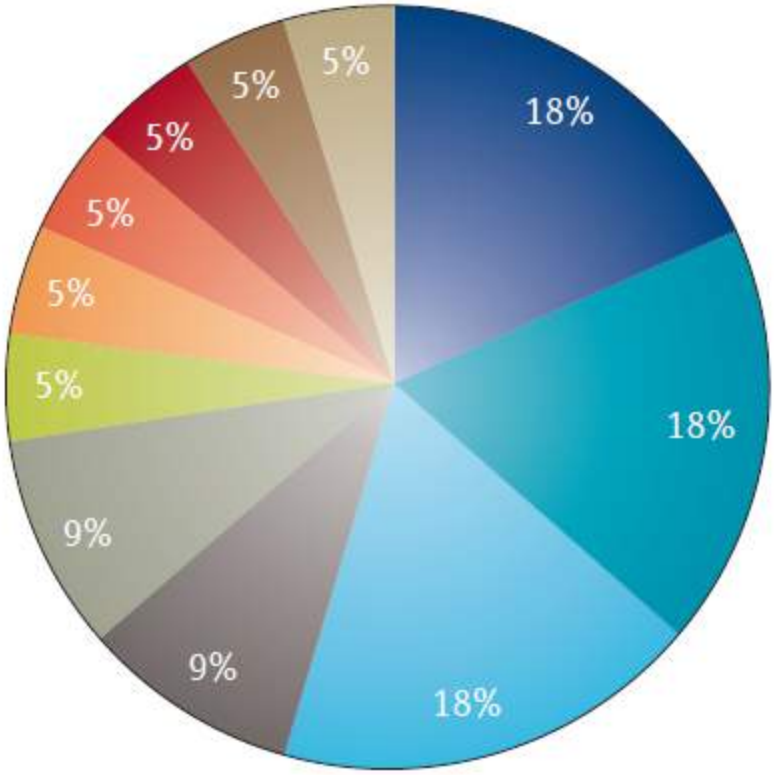
- *Spatio-Temporal Delivery*
  - *Long Acting Formulations*
  - *Enabling Sustained Target Tissue Concentrations*
  - *Mechanistic Understanding of Performance*

- *Summary and Conclusions*

Public

2016 Drug Approvals





- *High Growth Diseases areas include Infectious Disease, Oncology, and Neurology*
- *Continued investments in local diseases of the skin, eye and lungs (ca. 15%)*
- *Disease areas reflective of future growth Opportunities*

Nature Reviews, Drug Discovery, Vol 16, Feb 2017

Public

Value of 2016 Approvals

- *Increasing Price Pressure in US*
- *Intensified Competition in many therapeutic areas such as Diabetes and Oncology*

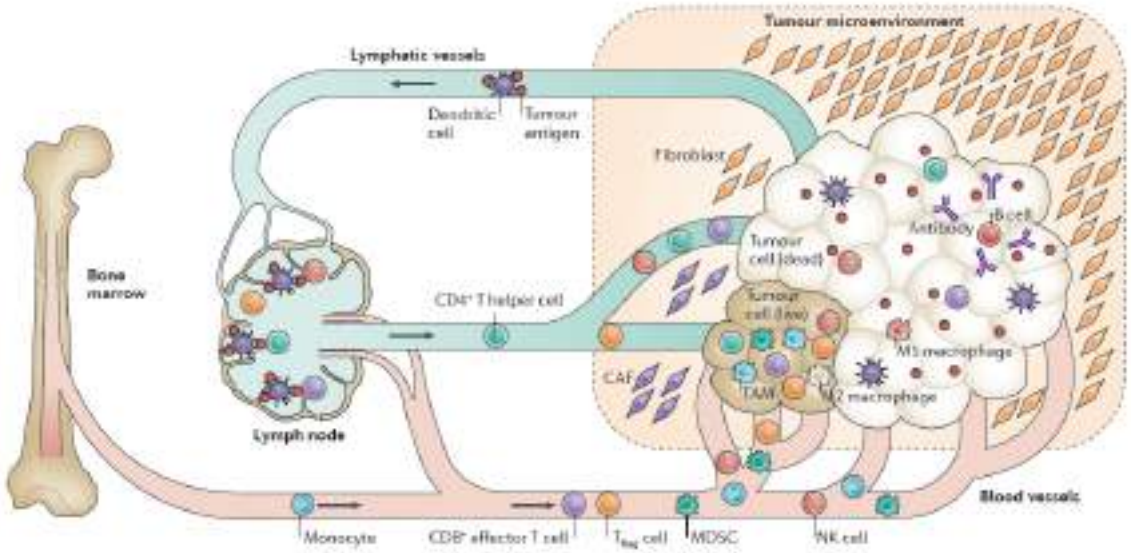
- *Improvements in Regulatory Process*
- *Deeper knowledge of Biology*
- *Growing Diversity in Modality*

Delivery

Nature Biobusiness briefs, Feb 2017

Public

Expanding Modalities in Immuno-Oncology



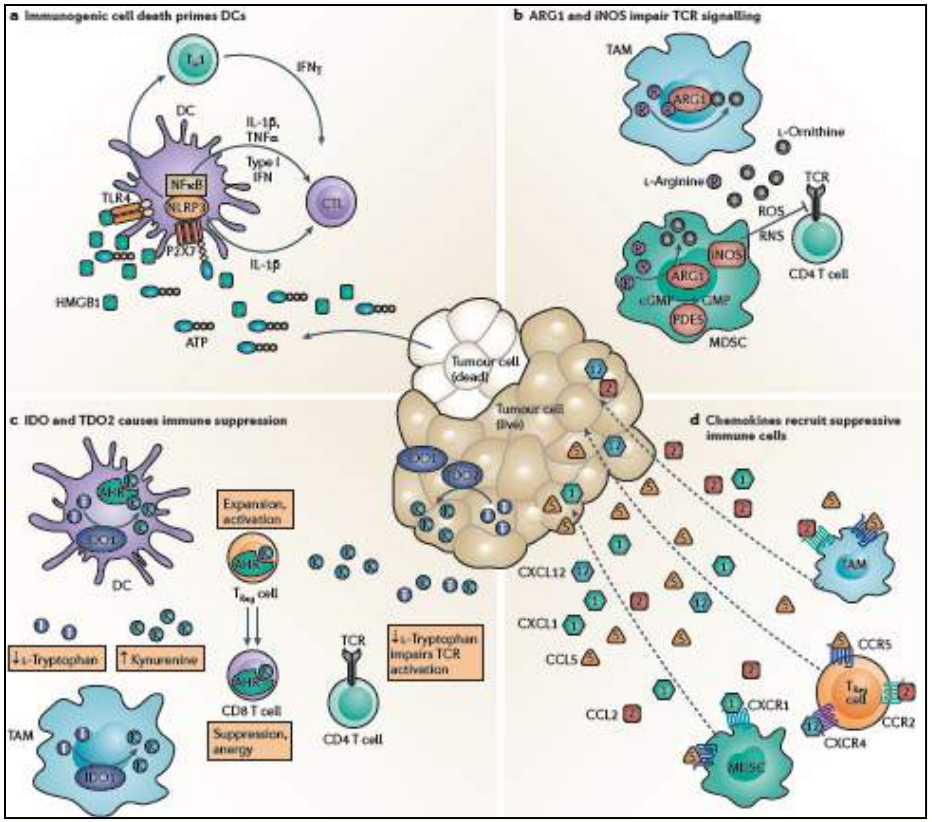
- *Increased Understanding of Tumor Biology, Immune Function and Immune Response to Cancer*
- *Expanding Modalities for Treatment and Prevention*

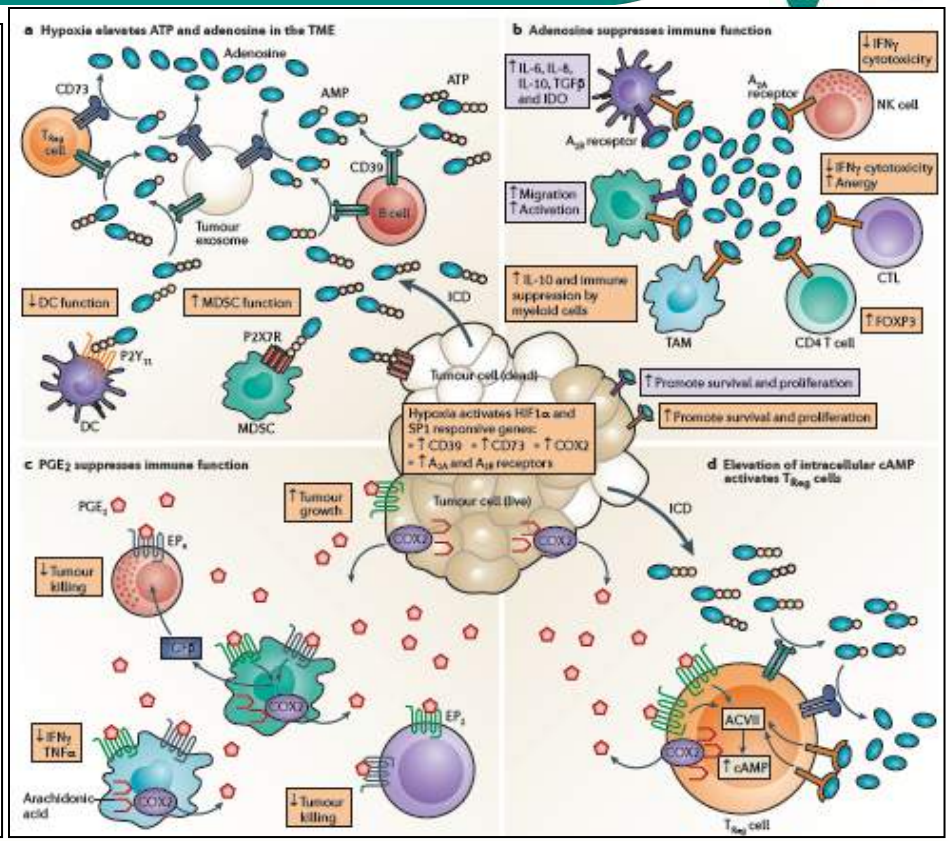
Vaccines	Prime patient immune response to tumour-specific antigens
Recombinant cytokines	Agonism or blockade of protein–protein immune pathways
mAbs	Highly selective agonism or blockade of extracellular protein–protein immune pathways; long half-life; non-immunogenic (human or humanized)
Autologous T cells	Tumour-targeted cytotoxicity of extracellular and intracellular tumour-specific antigens
Small molecules	Uniquely suited for intracellular targets, but also equally applicable to cell surface or extracellular targets

Public

Adams et al; Nature Reviews Drug Disc, Sep 2015

Expanding Target Space and Delivery Requirements in Immuno-Oncology



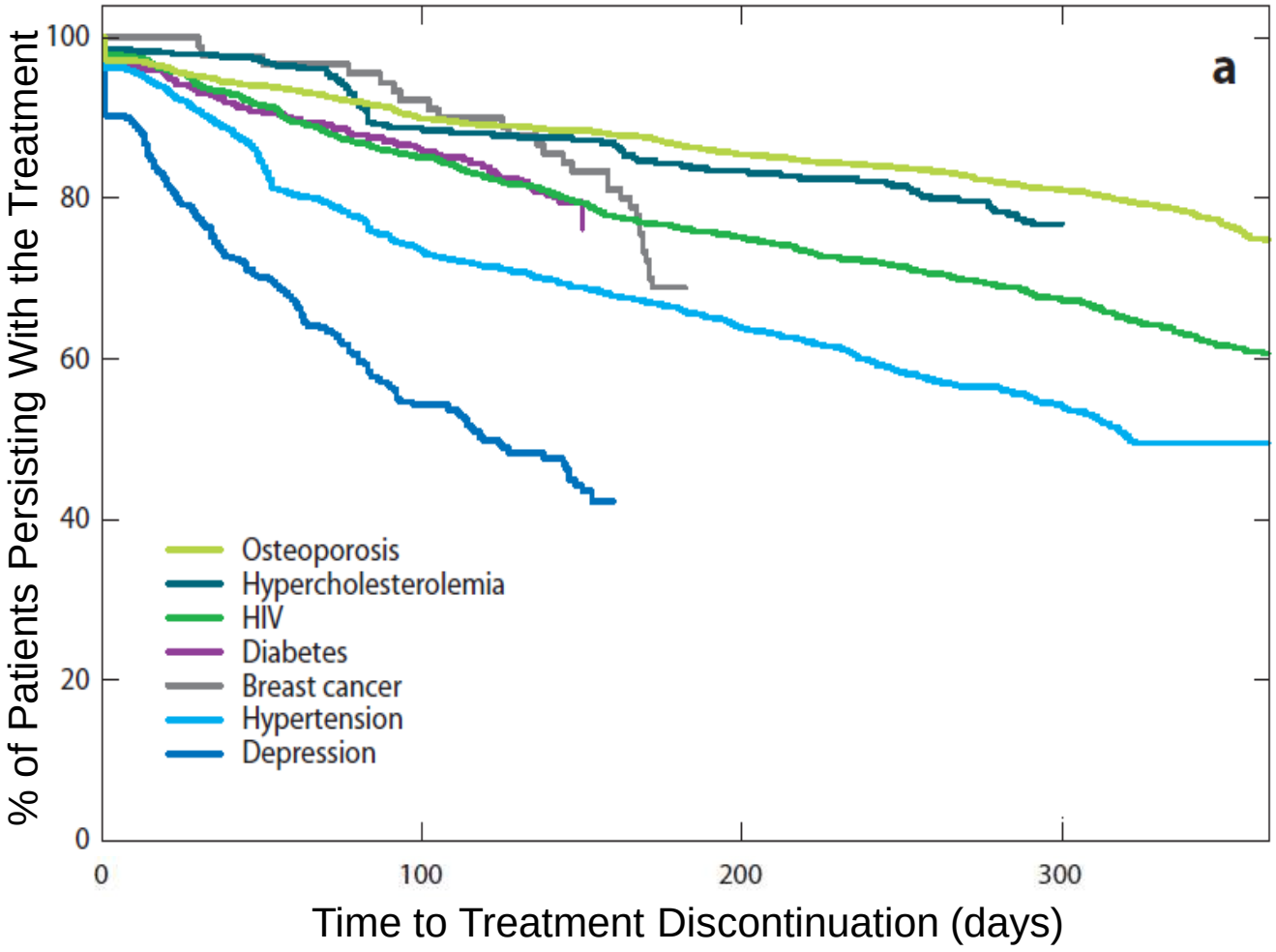


- *Growing Number of Targets under Clinical Interrogation*
- *Requirement to localize in TME, Innate Immune Cells or Inside Cells*

Public

Adams et al; Nature Reviews Drug Disc, Sep 2015

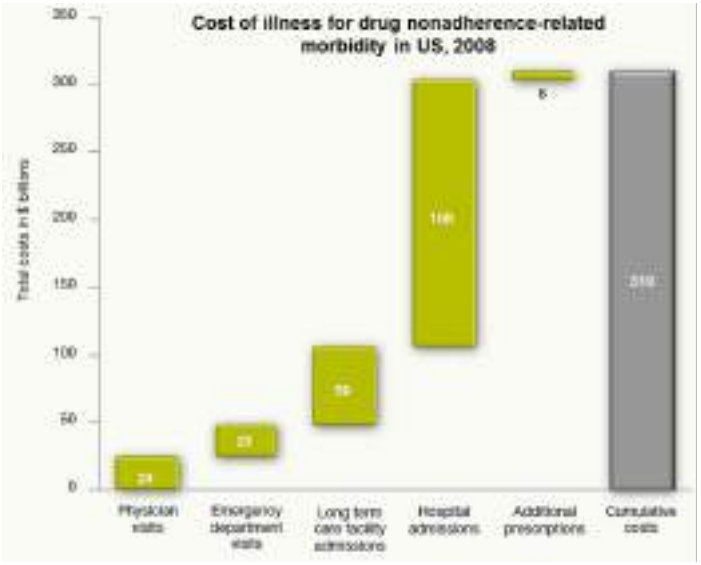
Adherence Rate Is Poor for Chronic Infectious Diseases and Neurological Disorders



Blaschke, et al. *Ann Rev Pharmacol Tox*. 2012;52:275-301.
Bates B. *Eularis*. March 2010.

Public

Long-Acting Parenterals (LAPs) Improve Cost-Effectiveness through Improved Adherence



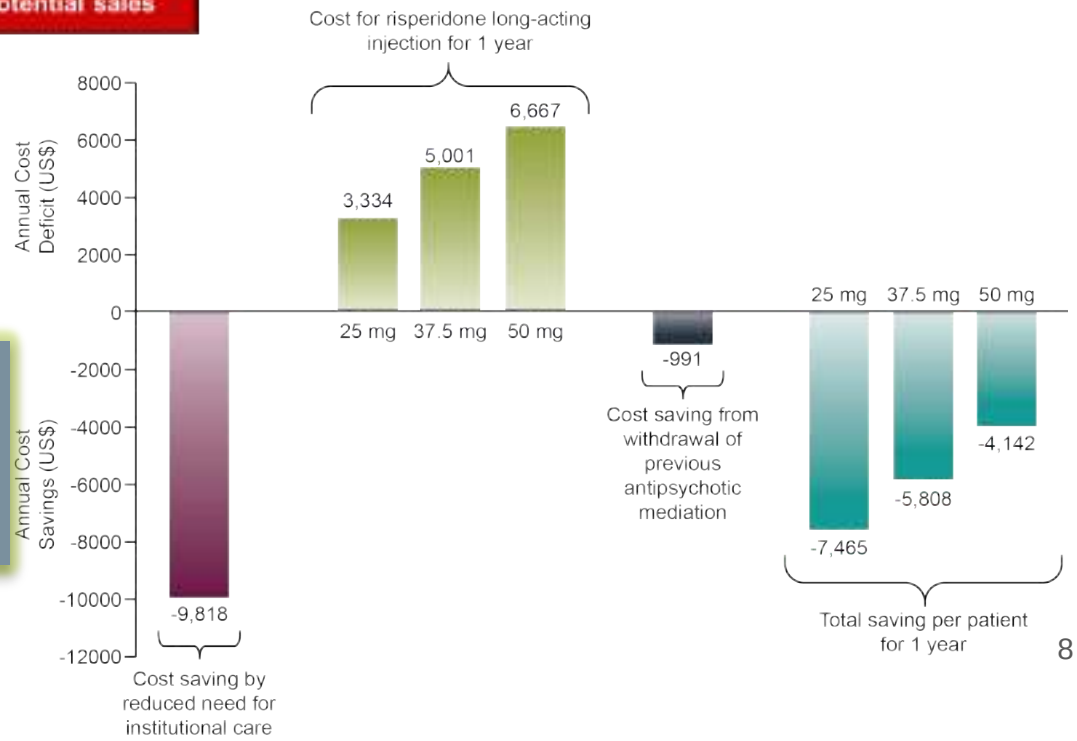
Cost of nonadherence = ~$310B annually

Nonadherence results in avg. per drug loss of 36% in potential sales

High Cost Impact of Non-adherence

Source: *Thinking outside the pillbox.*

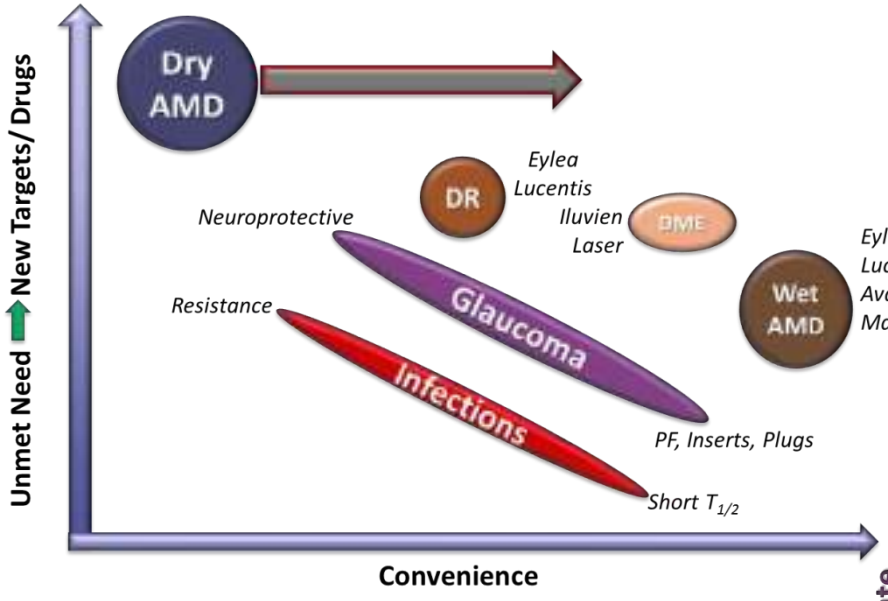
Cost-Effectiveness of Risperidone LAP (Risperdal Consta®)

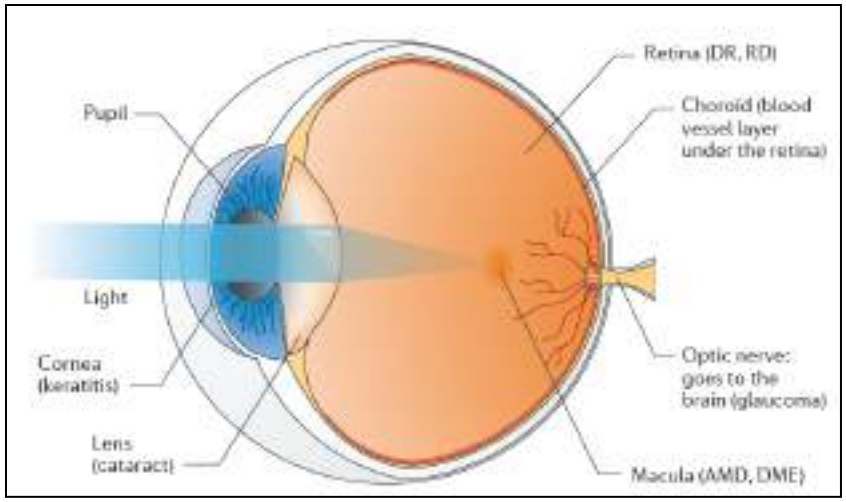


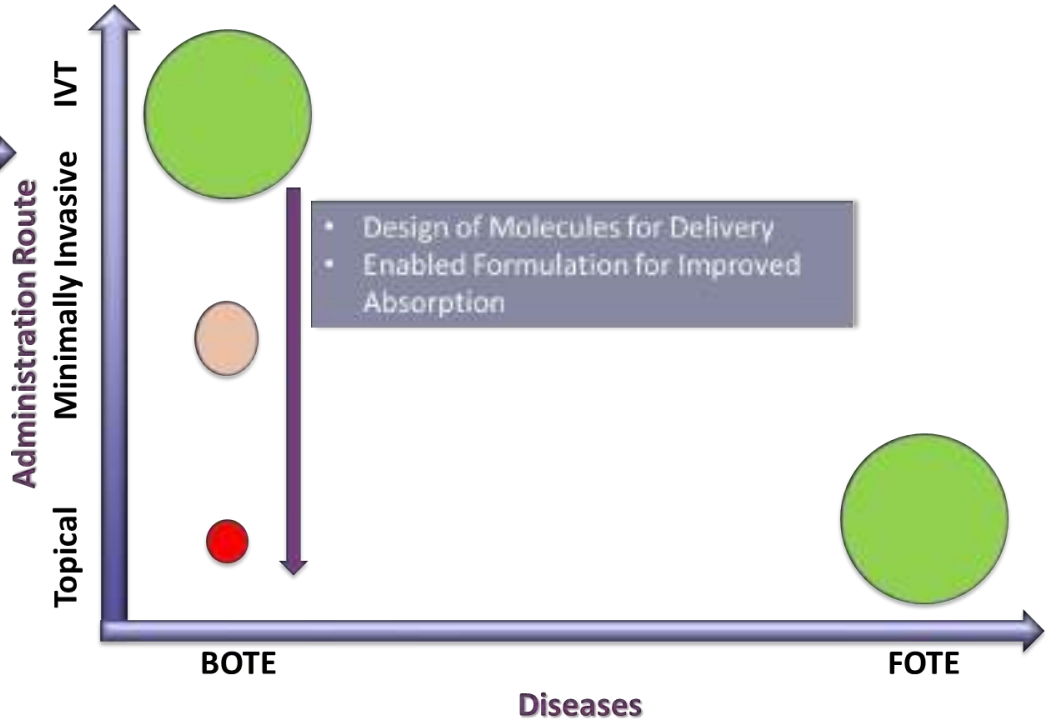
Chue P, Chue J. *Pharmacoecon Outcomes Res*. 2012;12(3);259-269.

Public

Significant Delivery Opportunity with Unmet Medical Needs for Ocular Diseases



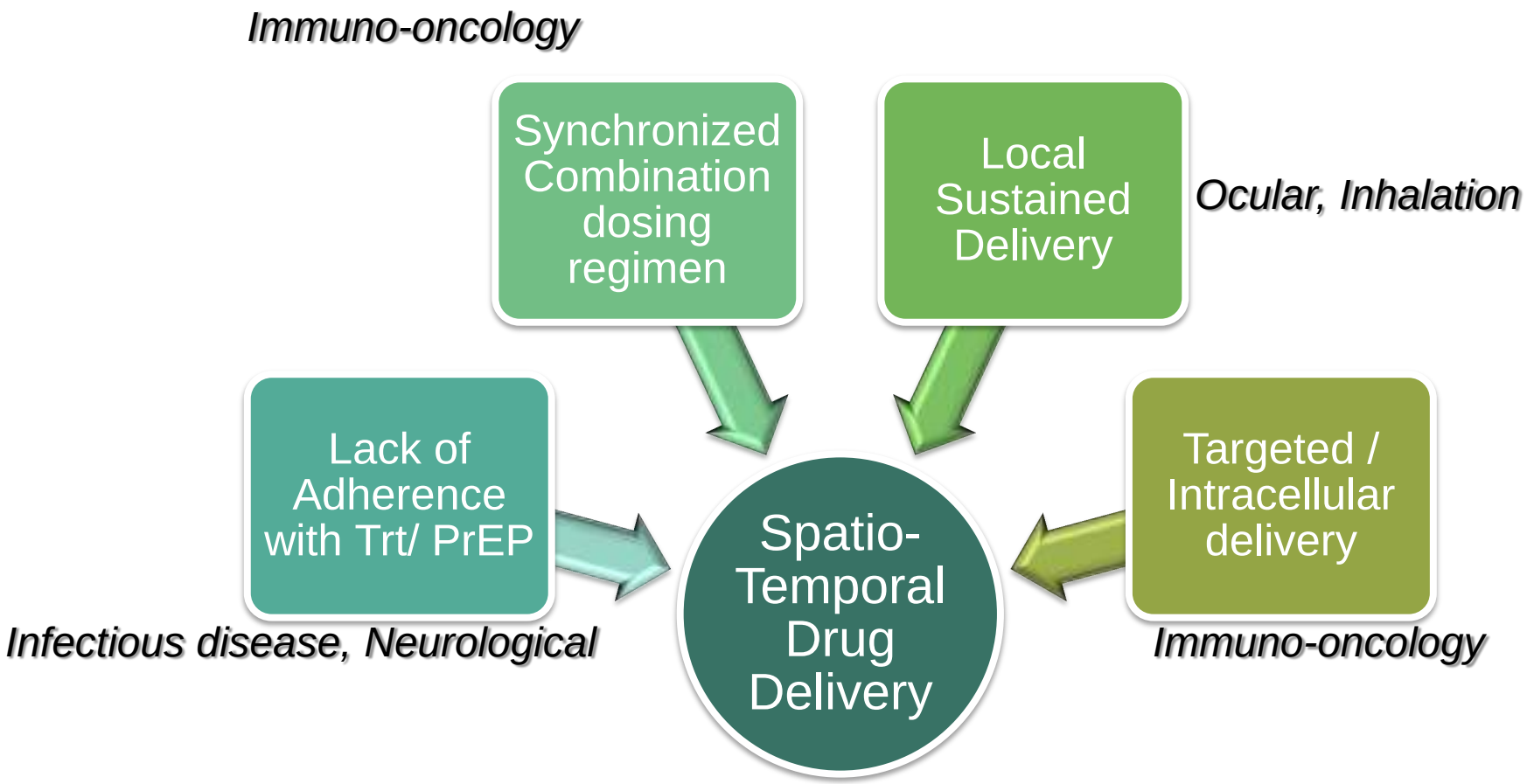




Nature Reviews, July 2012

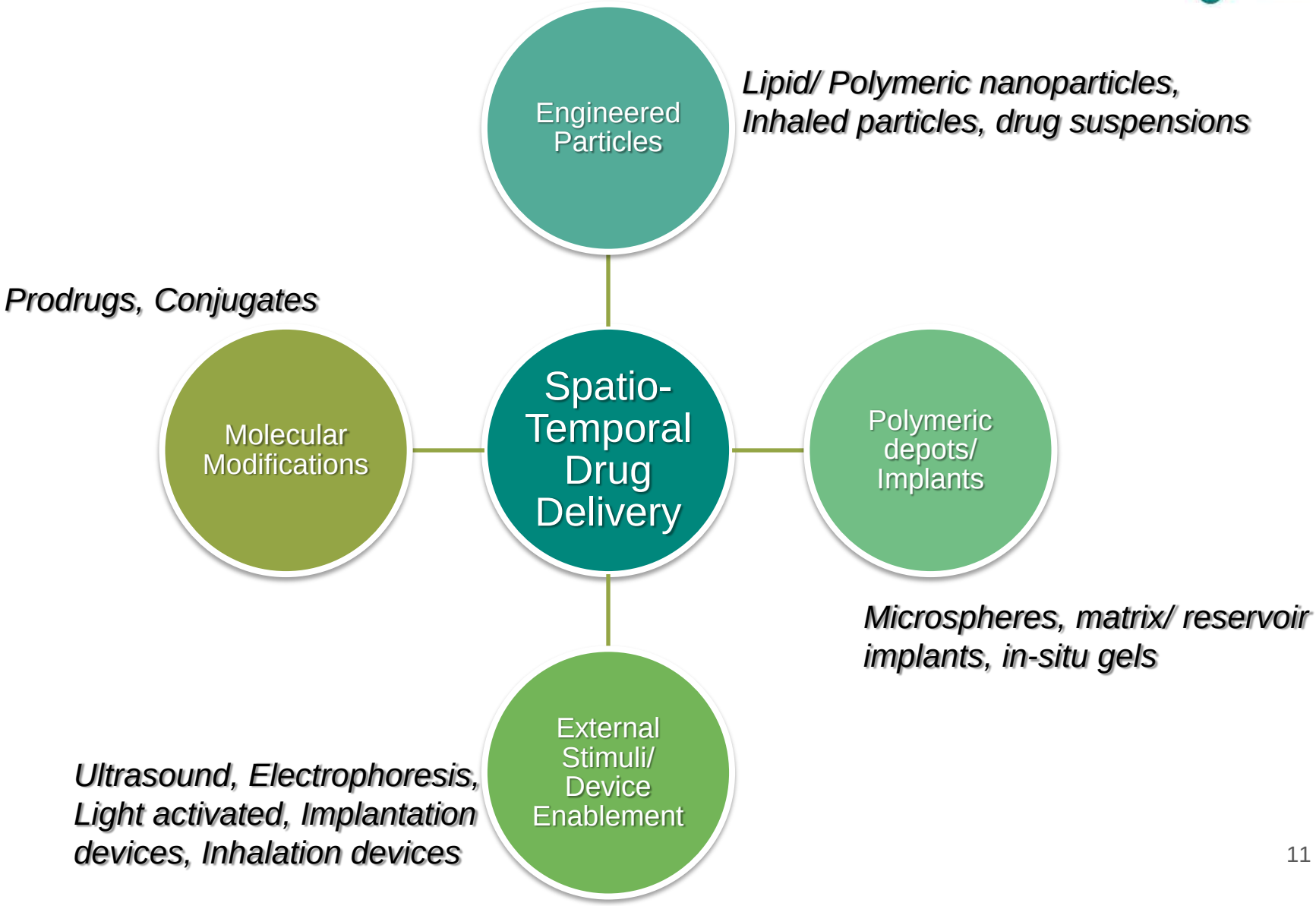
Public

High Growth Disease Areas Require Spatio-Temporal Drug Delivery to Maximize Patient Benefit



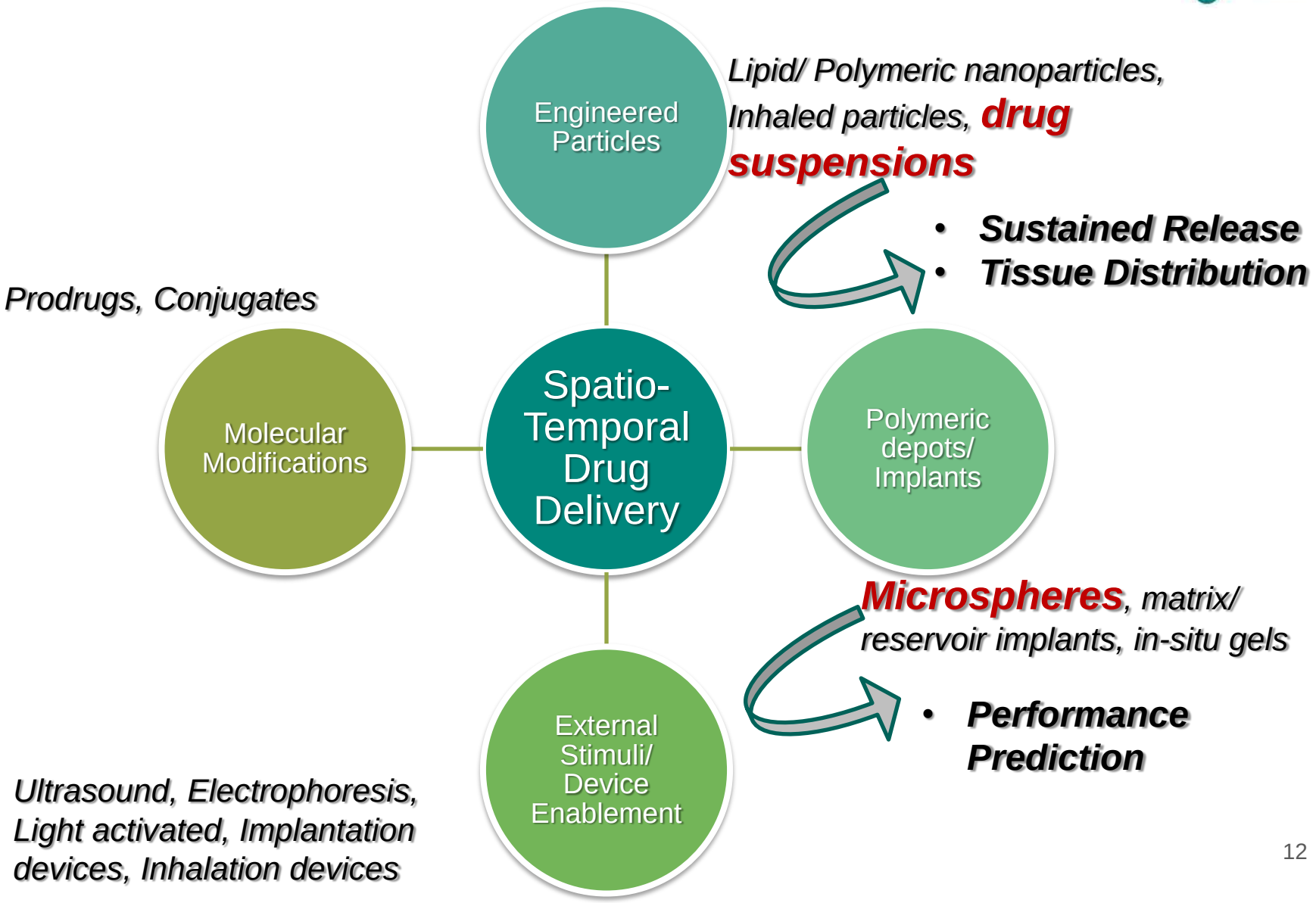
Public

Multiple Approaches Leveraged for Spatio-Temporal Drug Delivery



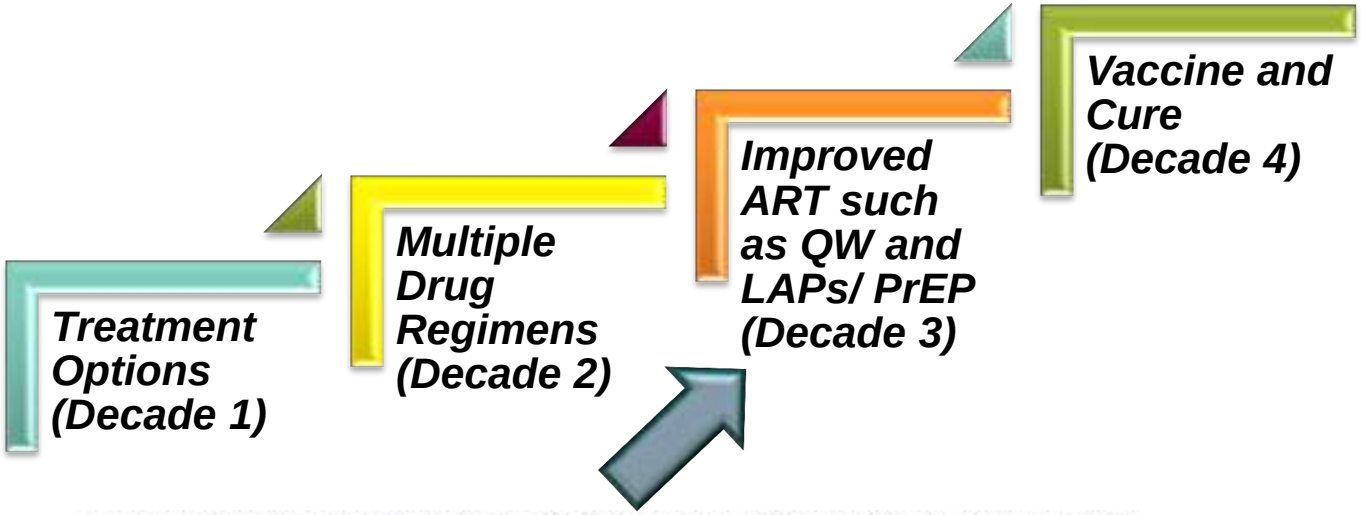
Public

Spatio-Temporal Drug Delivery: Opportunities/ Challenges

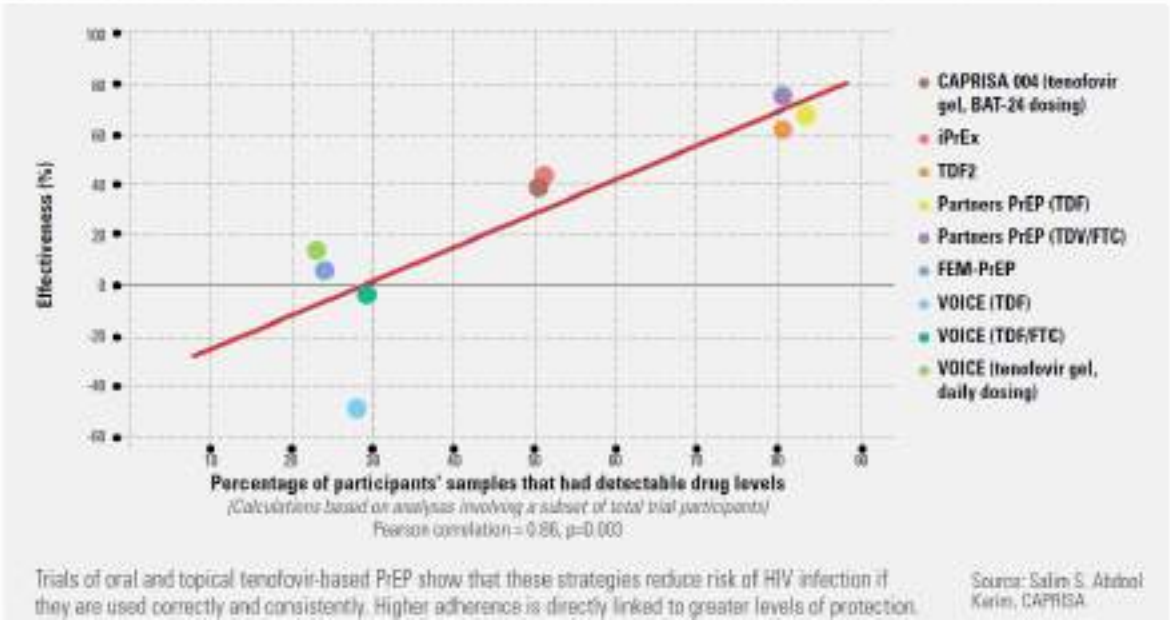


Public

Evolution of HIV Treatment and Prevention



Effectiveness and Adherence in Trials of Oral and Topical Tenofovir-Based Prevention

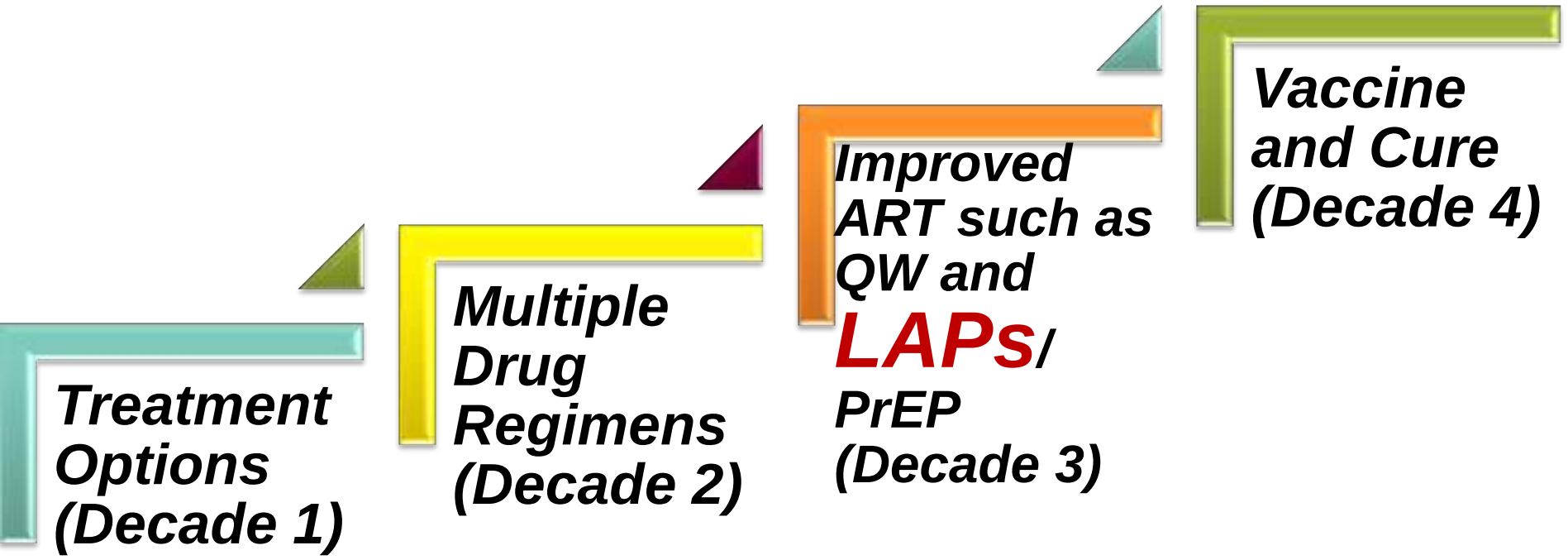


Trials of oral and topical tenofovir-based PrEP show that these strategies reduce risk of HIV infection if they are used correctly and consistently. Higher adherence is directly linked to greater levels of protection.

Source: Salim S. Abdool Karim, CAPRISA

Public

Evolution of HIV Treatment and Prevention

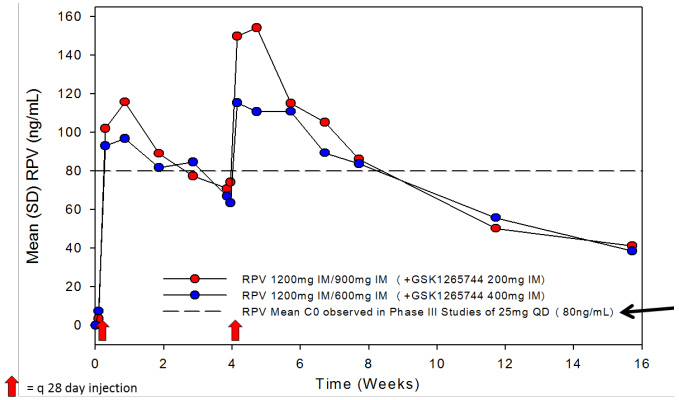


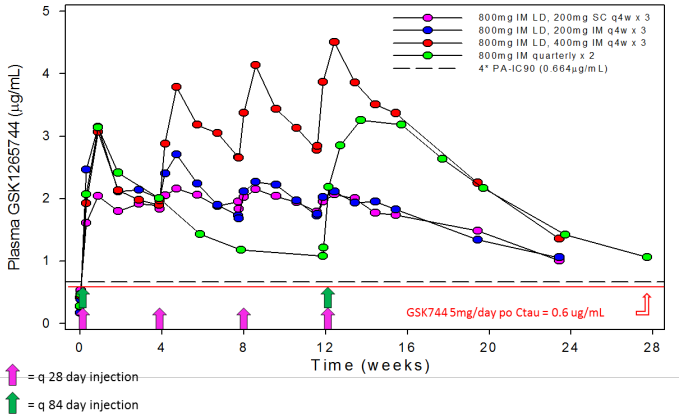
Public

ViiV/ Janssen Developing Cabotegravir/ Rilpivirine LAP for HIV Treatment/ Pre-exposure Prophylaxis

MSD

Rilpivirine 30% Nanosuspension	*LAP Suspensions*	Cabotegravir 20% Nanosuspension
600 mg QM (2 mL) 900 mg Q8W (3 mL)	*Phase 2 LATTE-2*	400 mg QM (2 mL) 600 mg Q8W (3 mL)
25 mg oral for 4 weeks 600 mg QM (2 mL) for 44 weeks	*Phase 3 FLAIR and ATLAS*	30 mg Oral for 4 weeks 400 mg QM (2 mL) for 44 weeks





Spreen, et al. 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention. July 2013; Kuala Lumpur, Malaysia. NCT02938520; NCT02951052

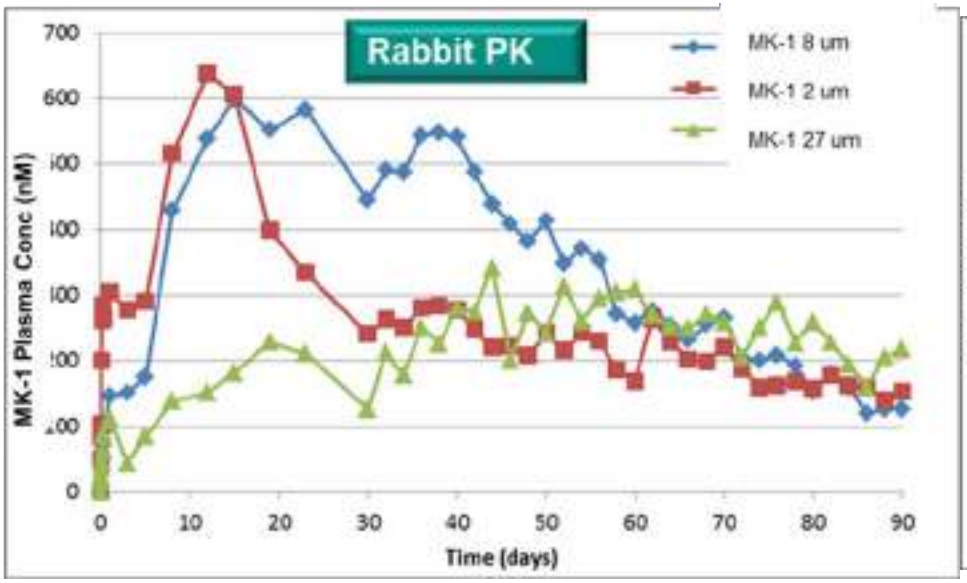
Public

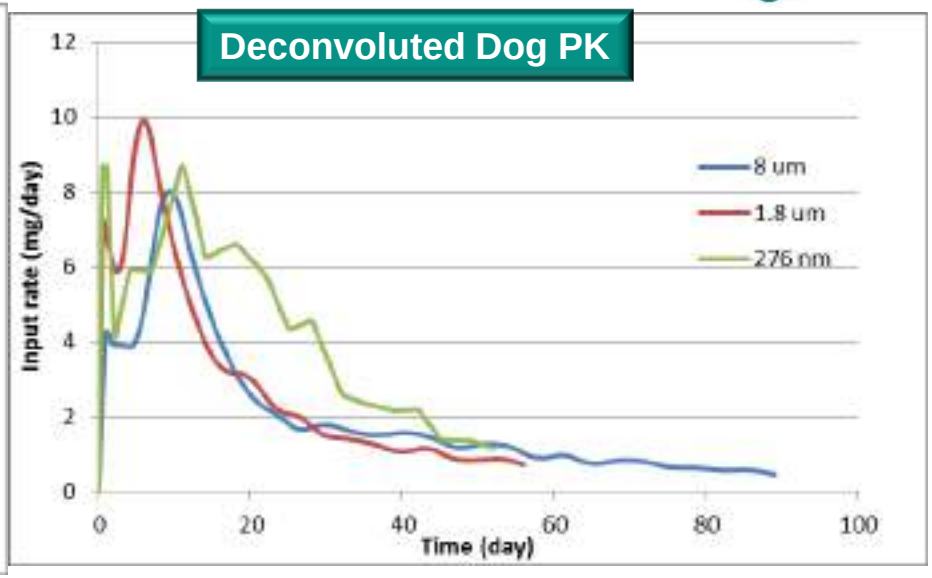
MK-1 Long Acting Parenteral Suspension (HIV)

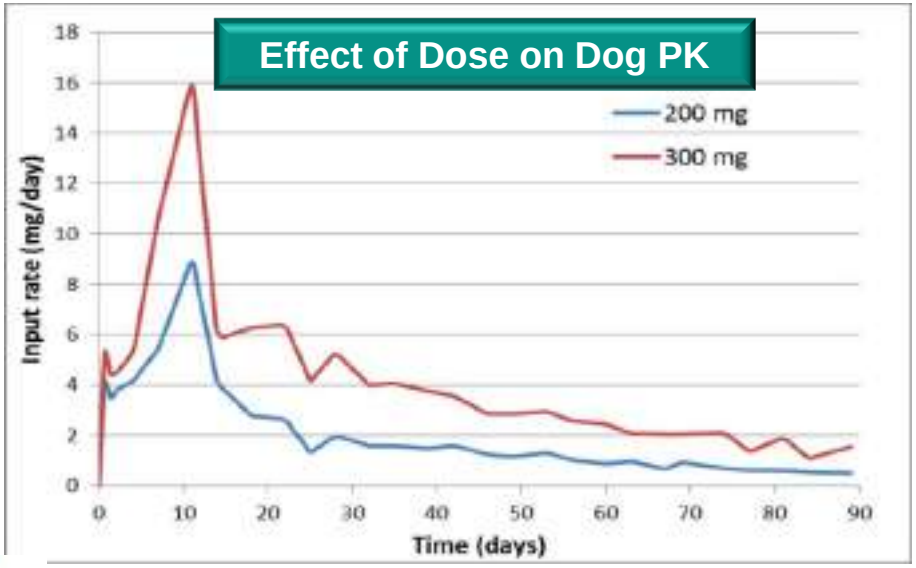
- Highly Crystalline Solid
- Low Aqueous Solubility (< 10 ug/mL)
- Daily Long-acting Dose projection: Approx 4.5 mg/day
  - Human Clearance vs efficacious trough levels required
- Sterile Microsuspensions and Nanosuspensions evaluated
  - Chemically and Physically Stable

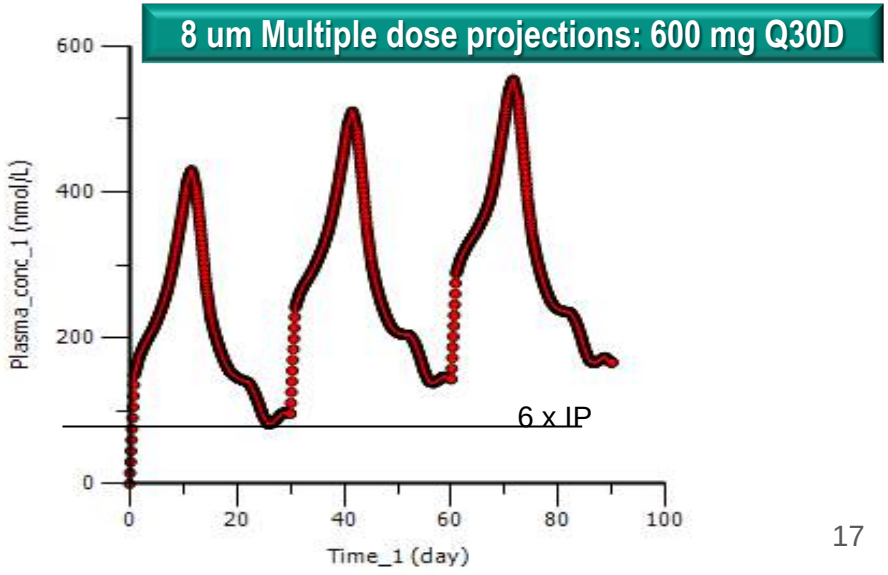
Public

MK-1 LAP Suspension Provides 2-3 Month Sustained Pharmacokinetics in Preclinical Studies



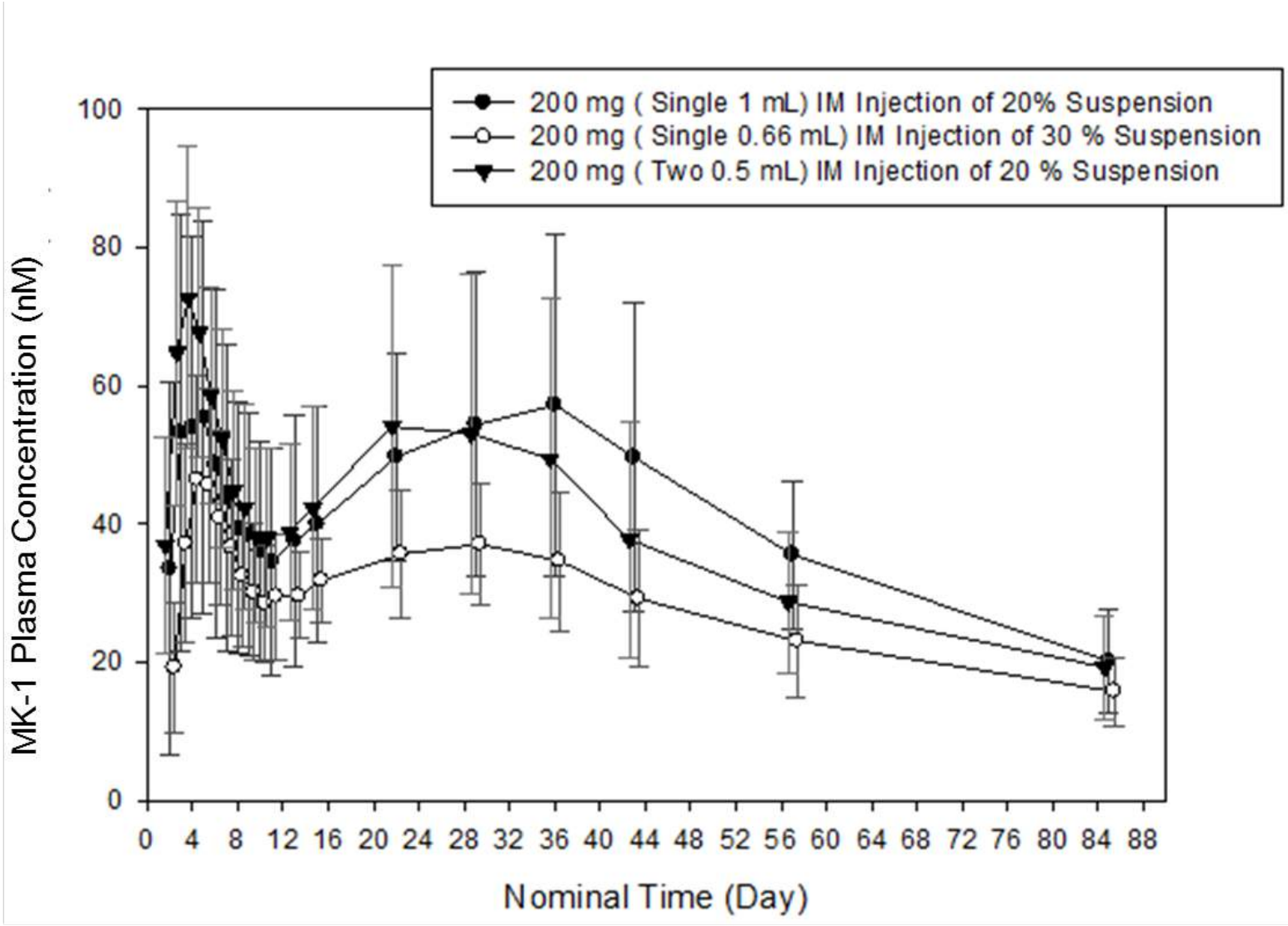






Public

MK-1 Long Acting Parenteral Suspension Provides Sustained Pharmacokinetics over >3 Months in Clinic

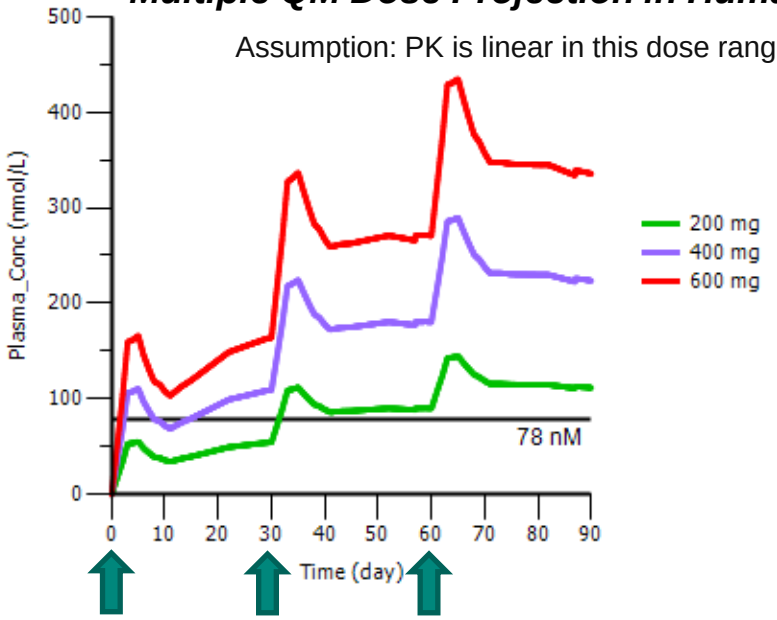


Public

MK-1 LAP Projected to be Efficacious @300 mg QM

Multiple QM Dose Projection in Humans

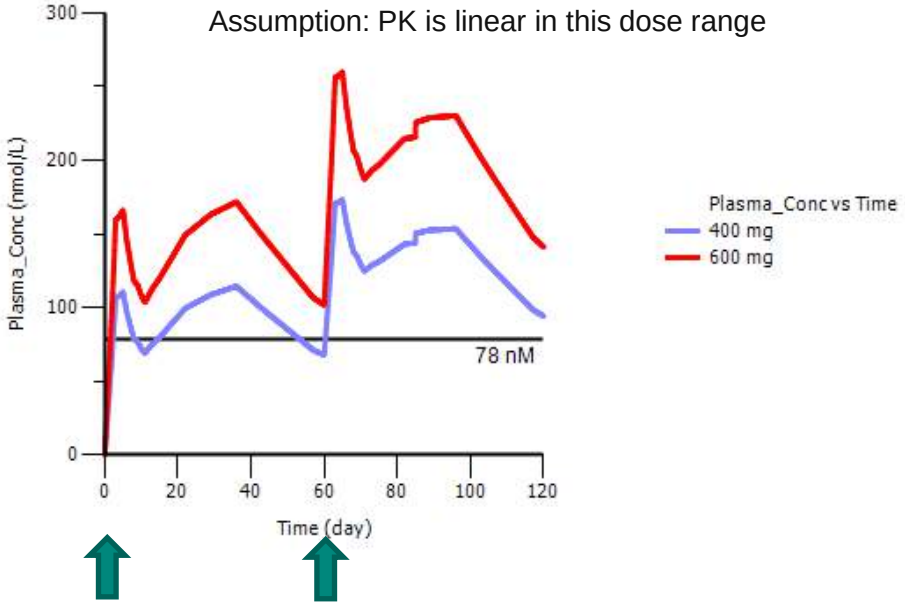
Assumption: PK is linear in this dose range



Arrows indicate the time of dose

Multiple Q2M Dose Projection in Humans

Assumption: PK is linear in this dose range



Arrows indicate the time of dose

A QM dose of ca. 300 mg or a Q2M dose of ca. 600 mg could be projected to be efficacious when stacked assuming linear PK vs dose response

HIV LAPs	Formulation	QM Dose Volume	Q2M Dose Volume
MK-1 LAP	30% microsuspension	1 mL (projected)	2 mL (projected)
Comparing to TMC278 and GSK 744	30% nanosuspension 20% nanosuspension	2 mL 2 mL	3 mL 3 mL

Public

Evolution of HIV Treatment and Prevention

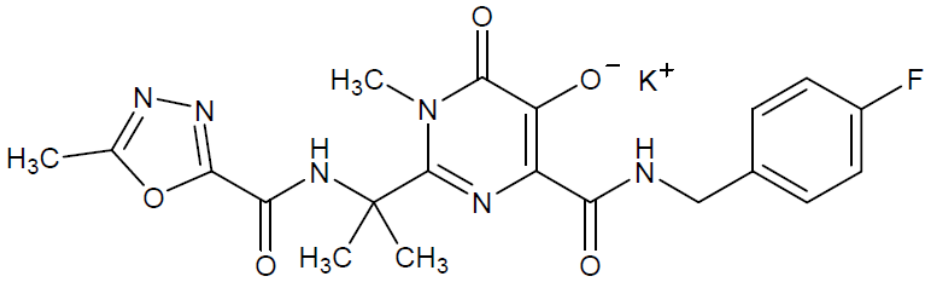
MSD

Treatment Options (Decade 1)

Multiple Drug Regimens (Decade 2)

Improved ART such as QW and LAPs/ PrEP (Decade 3)

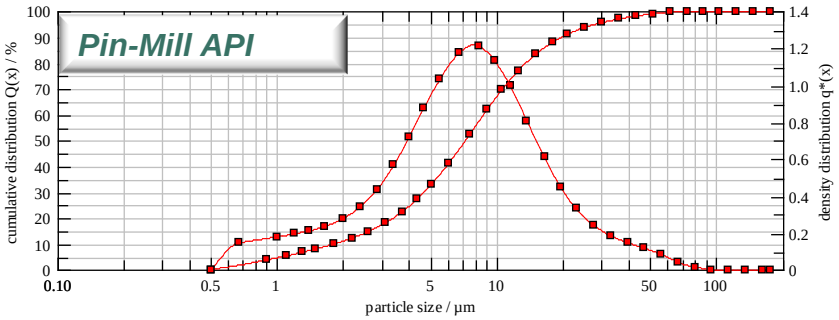
Vaccine and Cure (Decade 4)



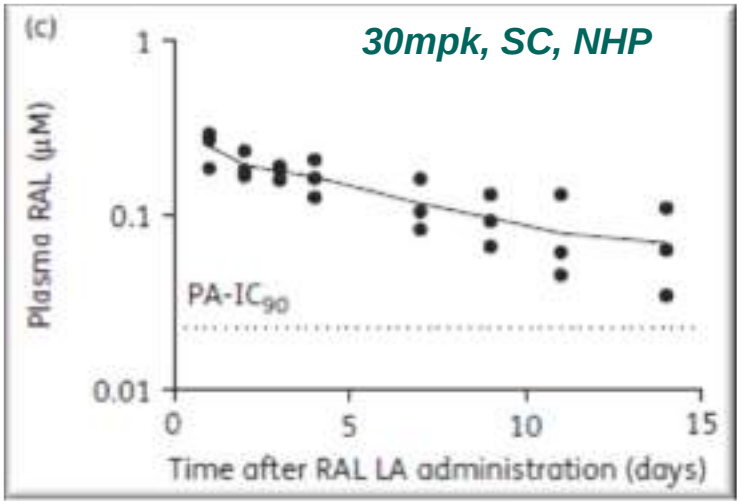
Name: Raltegravir (Isentress; 2007)
Mechanism: Integrase Strand Transfer Inhibitor (InSTI)
Route and Dose: Oral, 400 mg BID
Apparent terminal half-life – ca. 9 hrs
Delivery Need: Long-Acting PrEP with effective levels maintained in target tissues over sustained periods (Spatio-Temporal)

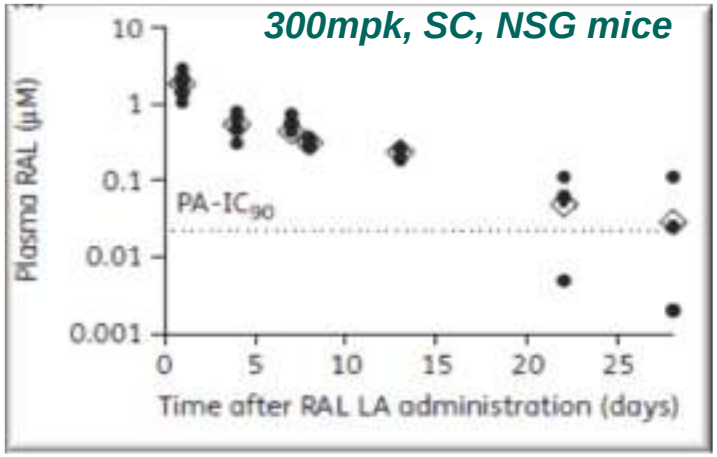
Public

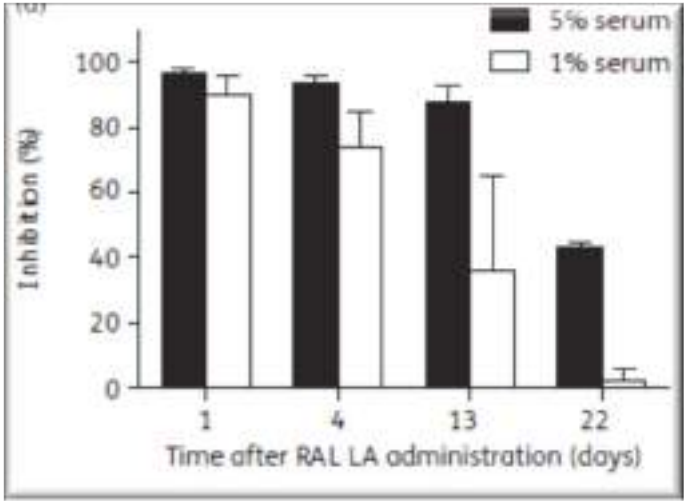
Raltegravir (InStI) LAP Suspension Sustains Effective Plasma Levels over 2-4 Weeks in NHP and Mice



Vehicle - 5% PEG 3350, 0.2% PS 80, 5% mannitol in water





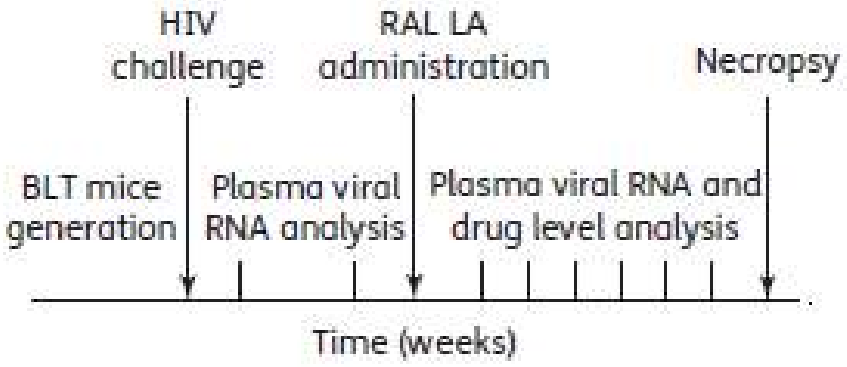


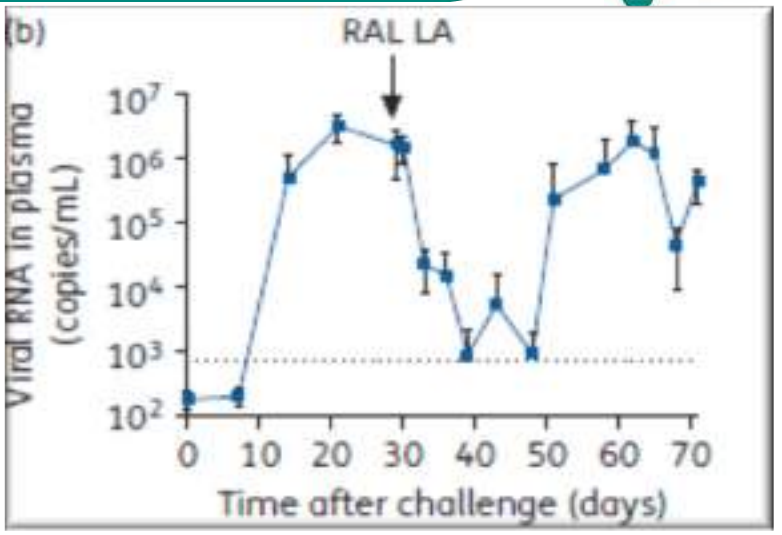
Public

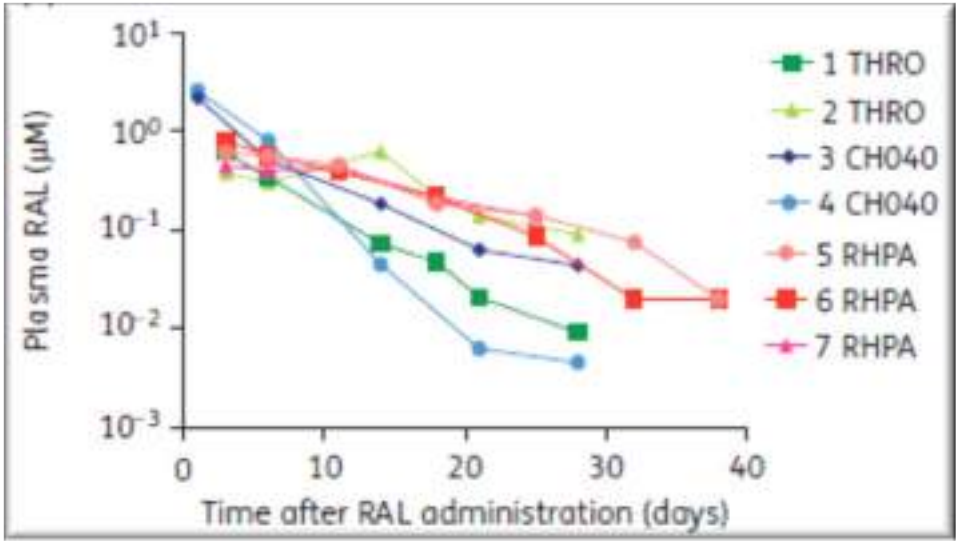
M. Kovarova et al, J Antimicrobial Chemotherapy, 2016

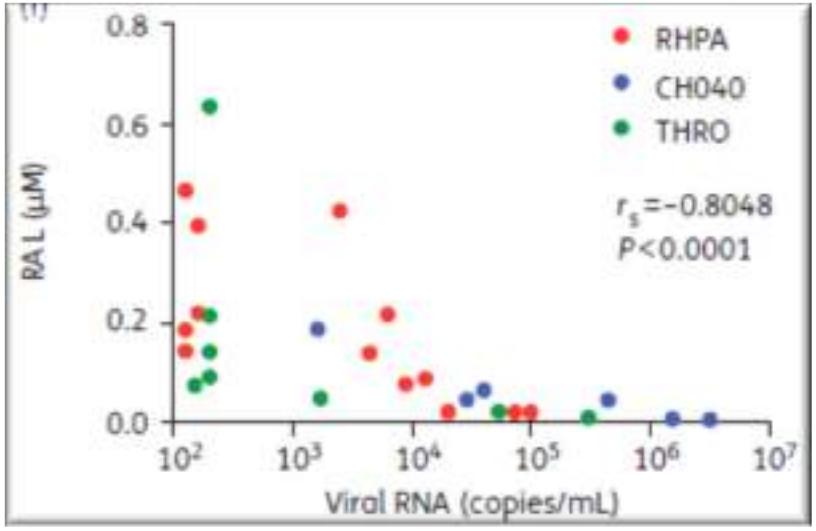
Formulations: Courtesy: Mittal et al

Raltegravir LAP Suppresses HIV-1 Replication in Infected Humanized BLT Mice







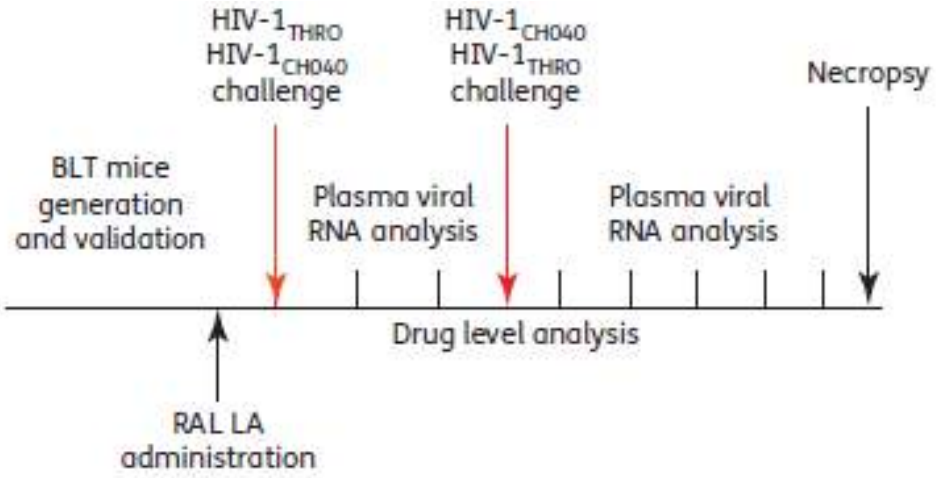


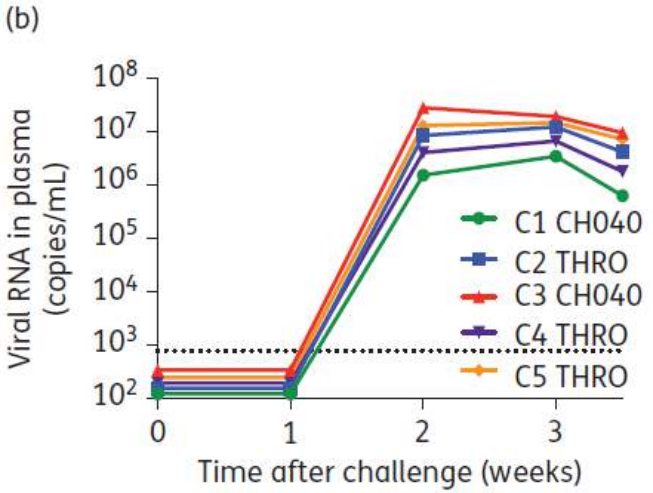
M. Kovarova et al, J Antimicrobial Chemotherapy, 2016

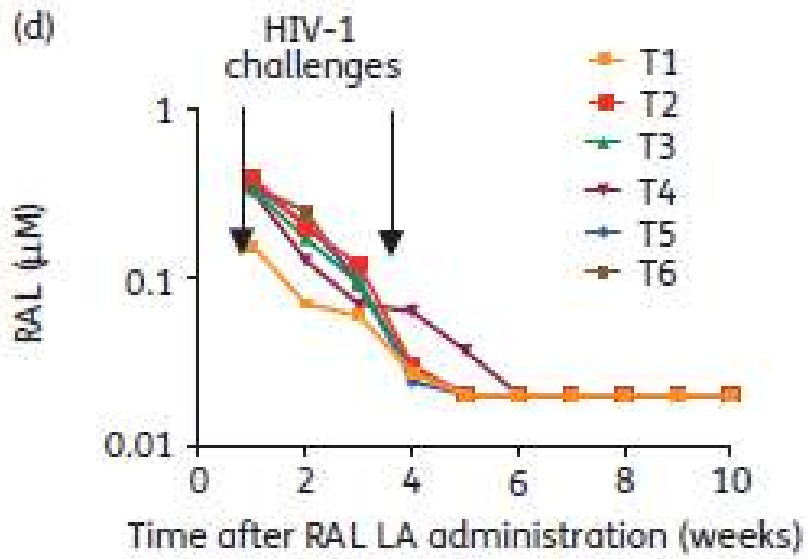
Formulations: Courtesy: Mittal et al

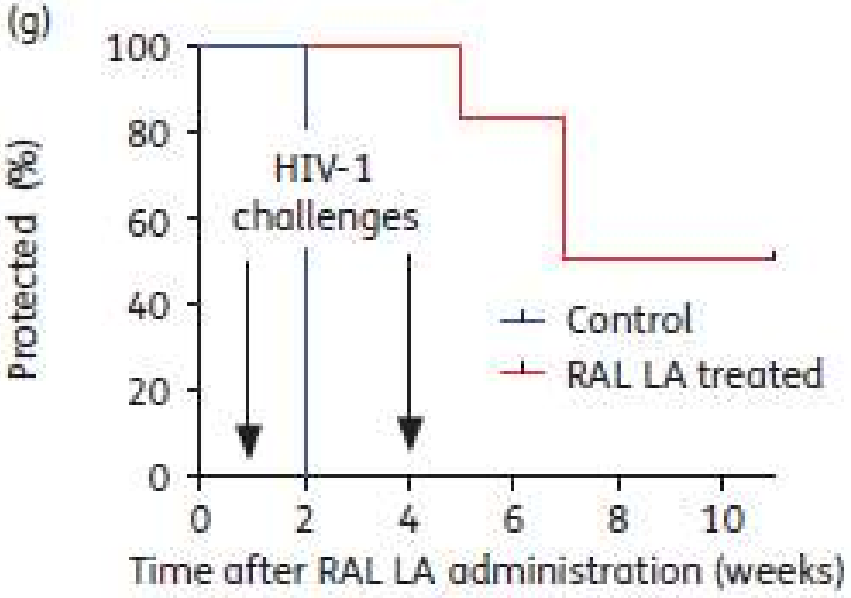
Public

Single SC Raltegravir LAP Dose Protects BLT Mice Against Two HIV Vaginal Challenges









M. Kovarova et al, J Antimicrobial Chemotherapy, 2016

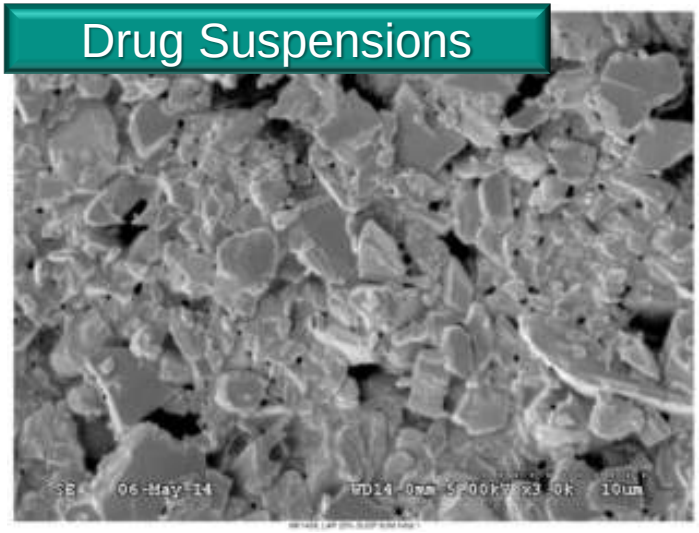
Formulations: Courtesy: Mittal et al

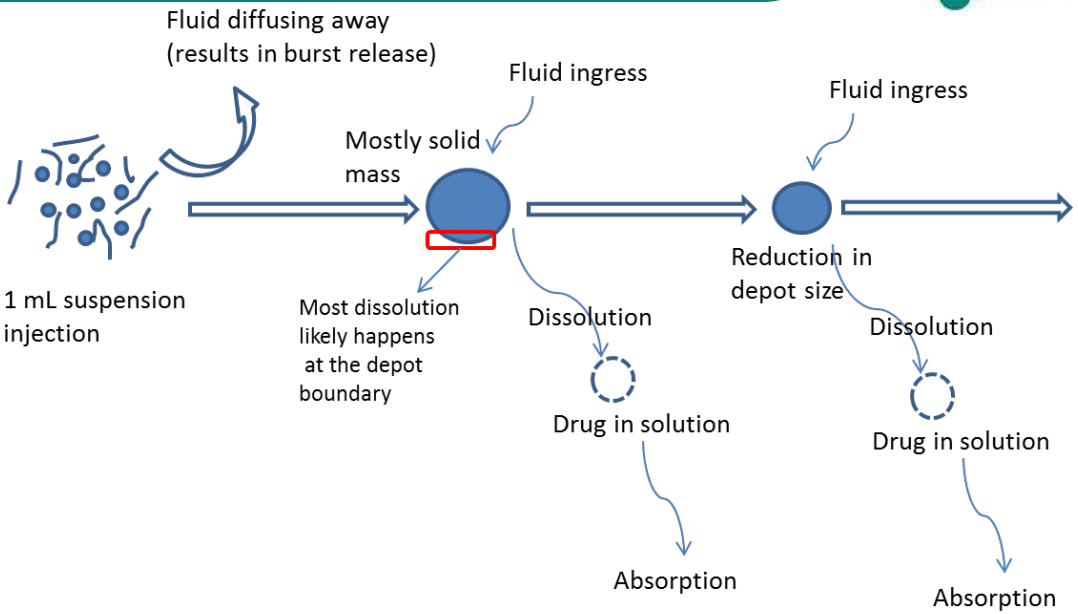
Public

Performance Prediction is a Challenge: In-vitro to Preclinical to Clinical Translation

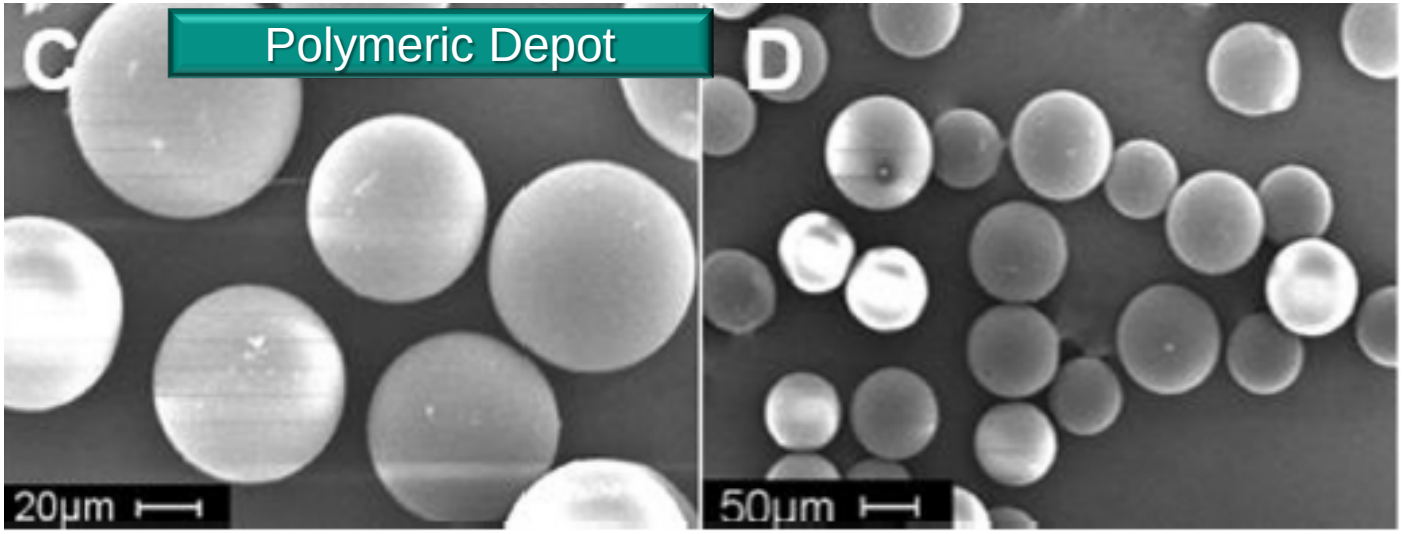
MSD

Drug Suspensions





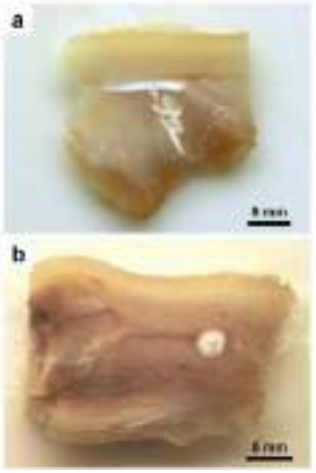
Polymeric Depot

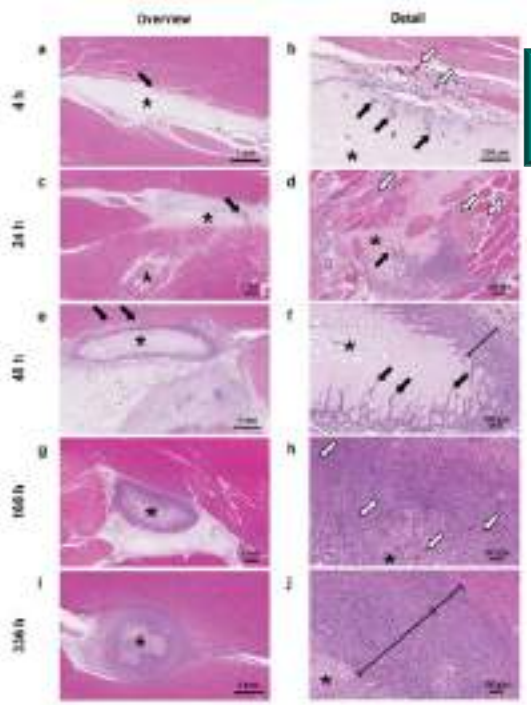


Public

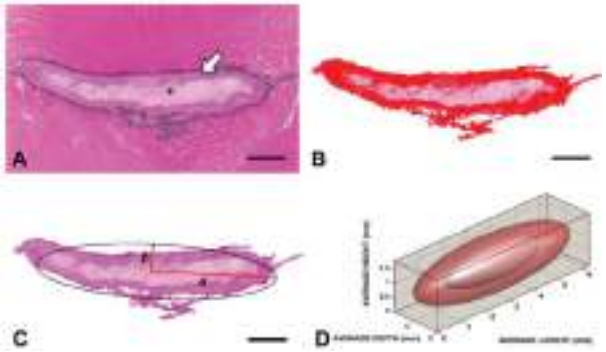
Understanding Time Course of Tissue Response to IM Injection of Suspension: Impact on Bioperformance

MSD

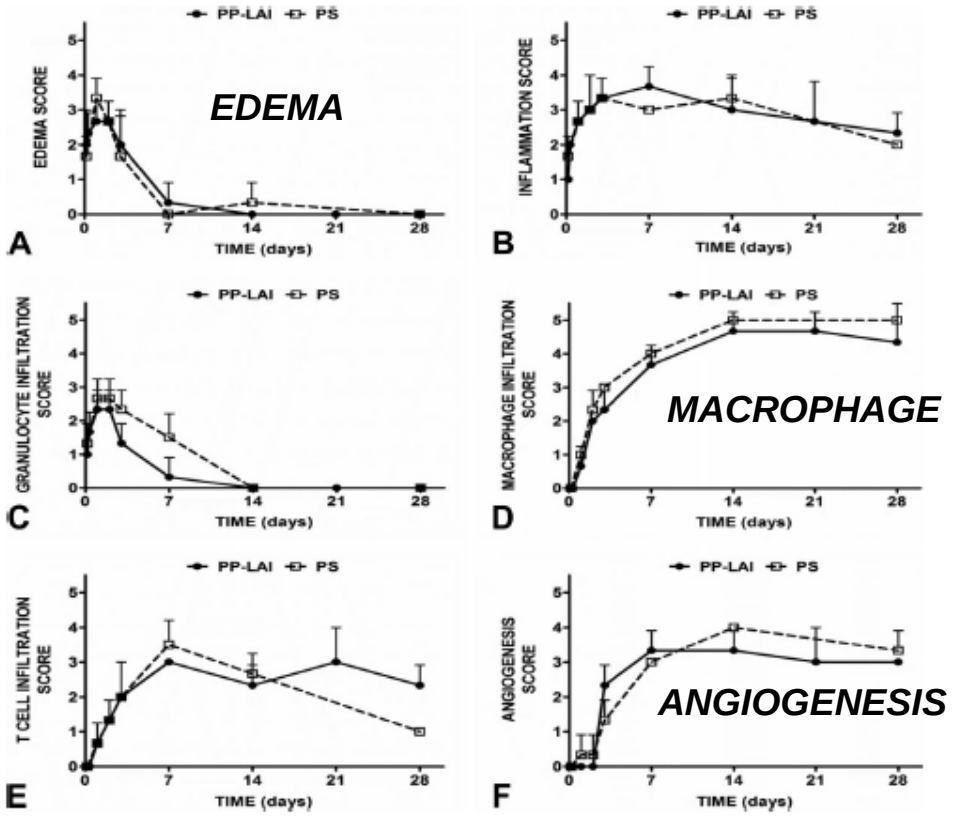




Depot Morphology



Time Course of Tissue Response Upon IM LAP Injection



Public

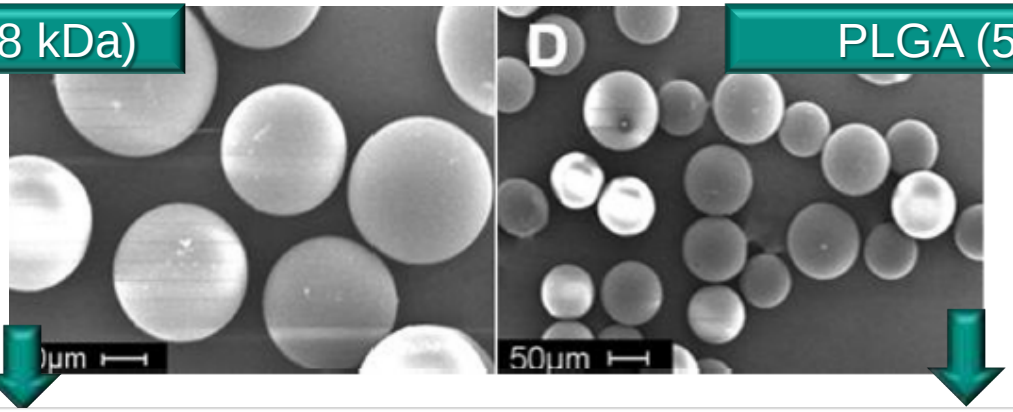
Darville N, et al. *J Pharm Sci*. 2014;103:2072-2087
Darville N. et al. Toxicologic Pathology, 2015.

Mechanistic Understanding of Triamcinolone Acetonide (TA) Release from PLGA Microspheres

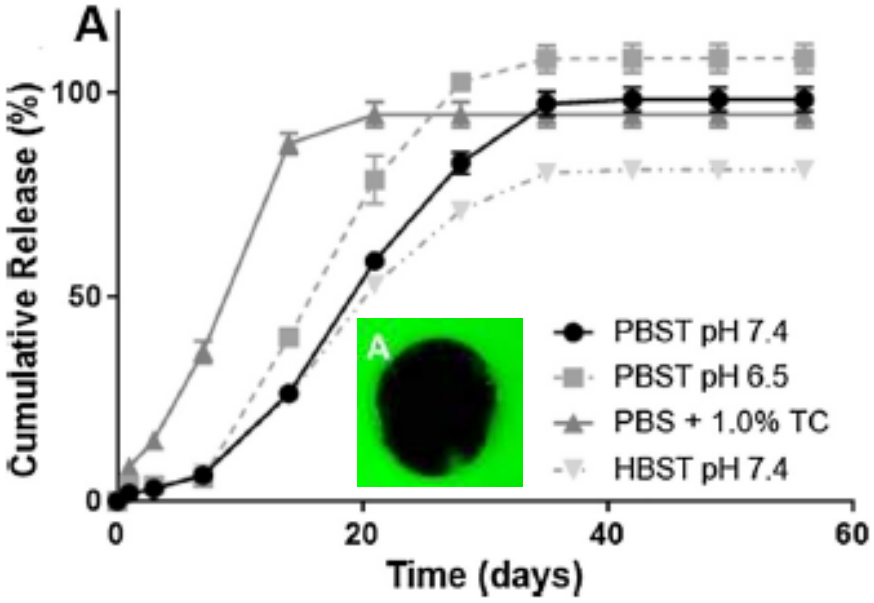
MSD

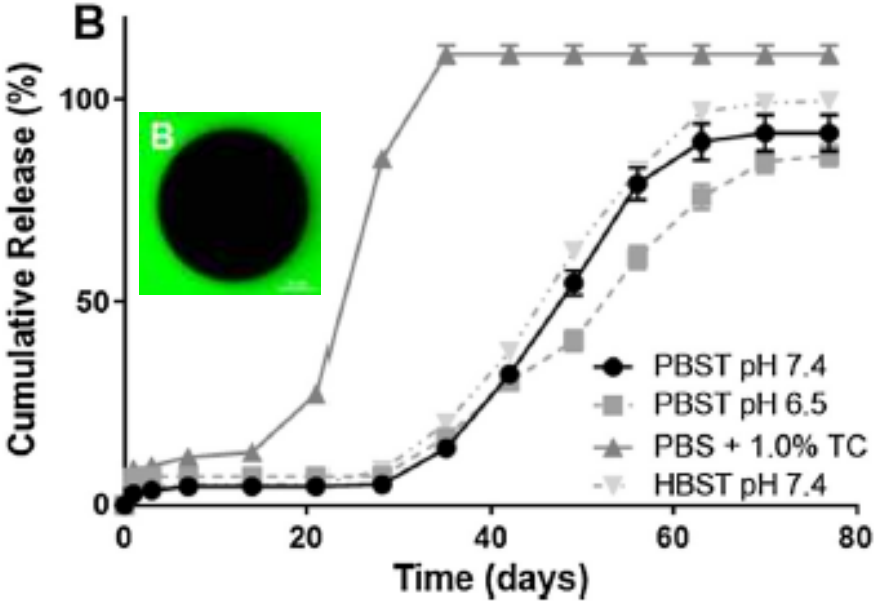
PLGA 502H (18 kDa)

PLGA (54 kDa)



In-Vitro Release of TA (5% DL) from PLGA Microspheres (S/O/W) as a f(release media)





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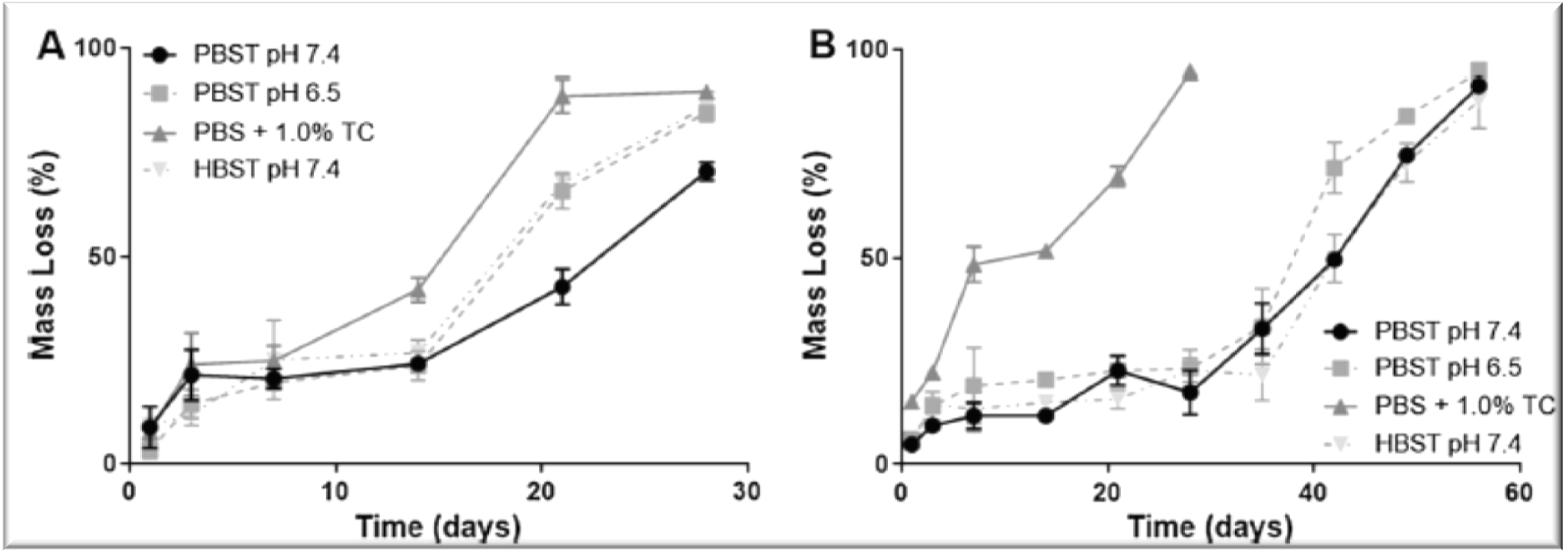
Doty, Mittal, Schwendeman et al, Eur J Pharm Biopharm, 2016

Understanding Polymer Mass Loss Kinetics as a *f*(Polymer Type, Buffer/ Media, pH)

PLGA 502H (18 kDa)

PLGA (54 kDa)



		PBST pH 7.4	PBST pH 6.5	PBS + 1.0% TC	HBST pH 7.4
Tr-A_1	$t_{50,release}$	19.0 ± 0.4	16.6 ± 0.4	8.0 ± 0.4*	17.6 ± 0.2
	$t_{50,erosion}$	25 ± 8	18.6 ± 0.8	15 ± 1	18 ± 2
	$t_{50,release}/t_{50,erosion}$	**0.77**	**0.89**	**0.52**	**0.96**
Tr-A_2	$t_{50,release}$	46.8 ± 0.6	50.1 ± 0.8	25.0 ± 0.3*	46.1 ± 0.3
	$t_{50,erosion}$	46 ± 3	39 ± 2	18 ± 2*†	43 ± 2
	$t_{50,release}/t_{50,erosion}$	**1.02**	**1.28**	**1.43**	**1.06**

* $p < 0.05$ compared to PBST pH 7.4.
† linear regression was used.

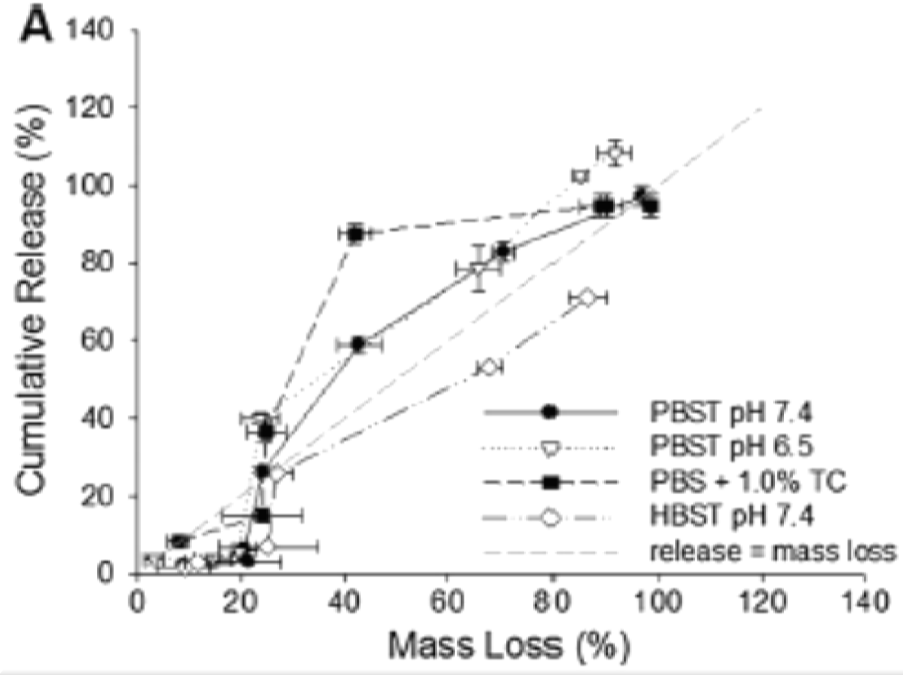
Public

Doty, Mittal, Schwendeman et al, Eur J Pharm Biopharm, 2016

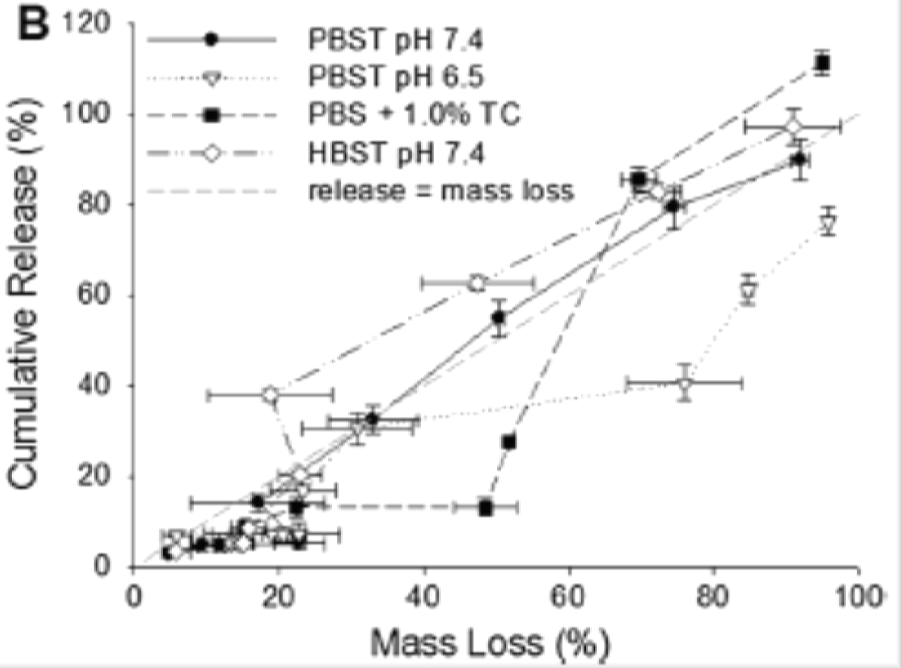
Understanding Mechanism of Release: Correlating In-Vitro Release to Polymer Mass Loss Kinetics

MSD

PLGA 502H (18 kDa)



PLGA (54 kDa)

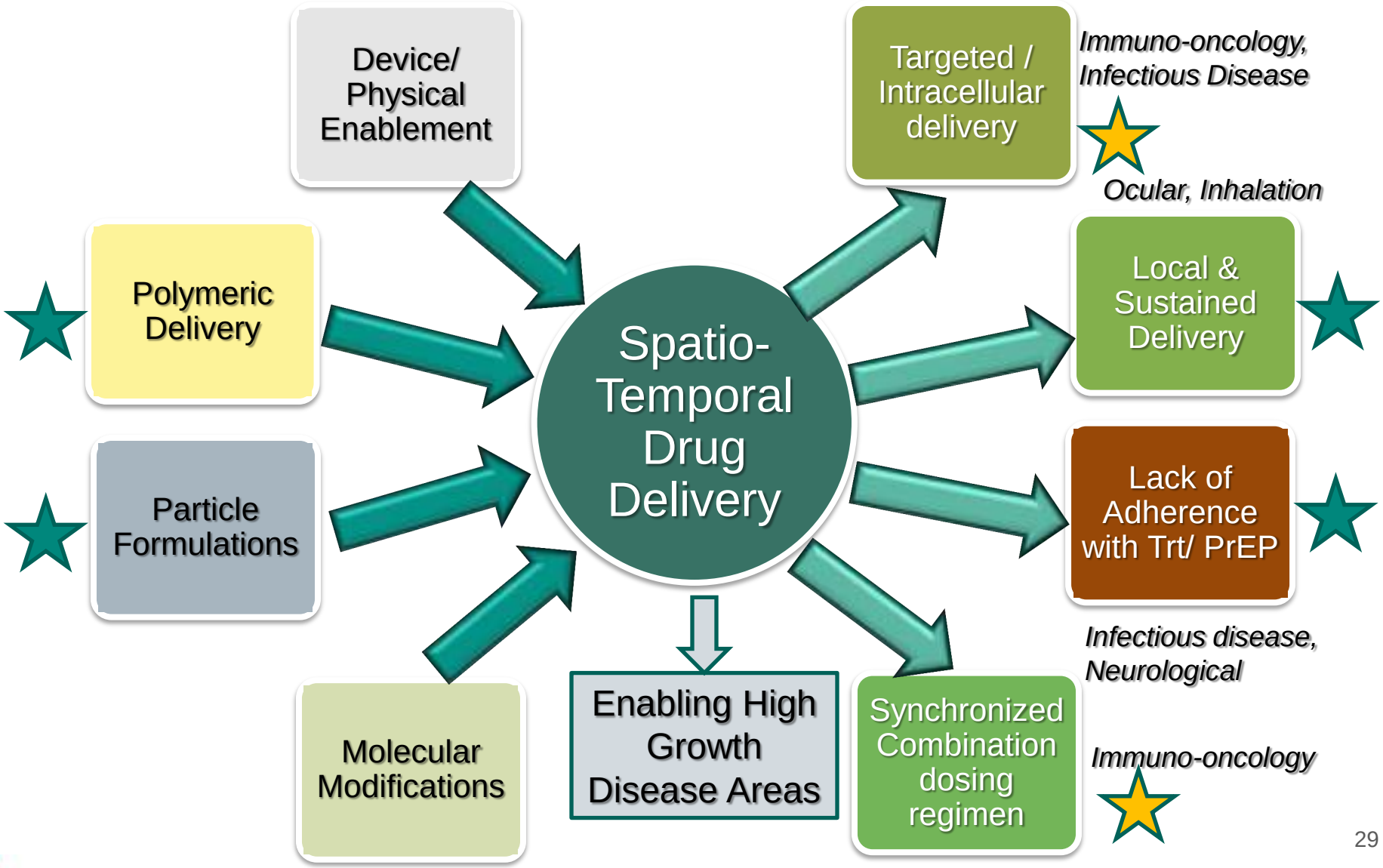


- ***Low Molecular weight acid-terminated PLGA Formulations: Erosion + Diffusion through Polymer (w/ TC)***
- ***Moderate Molecular weight ester-capped PLGA Formulations: Erosion***
- ***Next Step: Release Mechanism in vivo and mechanistic strategies for IVIVCs***

Public

Doty, Mittal, Schwendeman et al, Eur J Pharm Biopharm, 2016

Summary and Conclusions



Public

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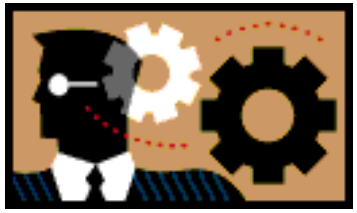

1 Formerly at Oss, Netherlands
2 Now with Pfizer
3 Now with Sandoz
4 Now Retired

QUESTIONS

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