Intra-Lesional Approaches

Regulatory Issues

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Disclosures

Funding

Checkmate Pharmaceuticals (Regeneron)

Pfizer

Founder and CEO

LIRECAP

Intralesional therapy of cancer
Not a new concept

Dr. William Coley – 1891

- Observed 7 year old girl who experienced regression of a tumor in her neck after infection
- Heard of other cases
- Injected tumors with live, then killed bacteria
- Significant responses but also toxicity

Two decades of research
Predated human subjects or regulatory oversight
Limited reproducibility
No understanding of mechanism

New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

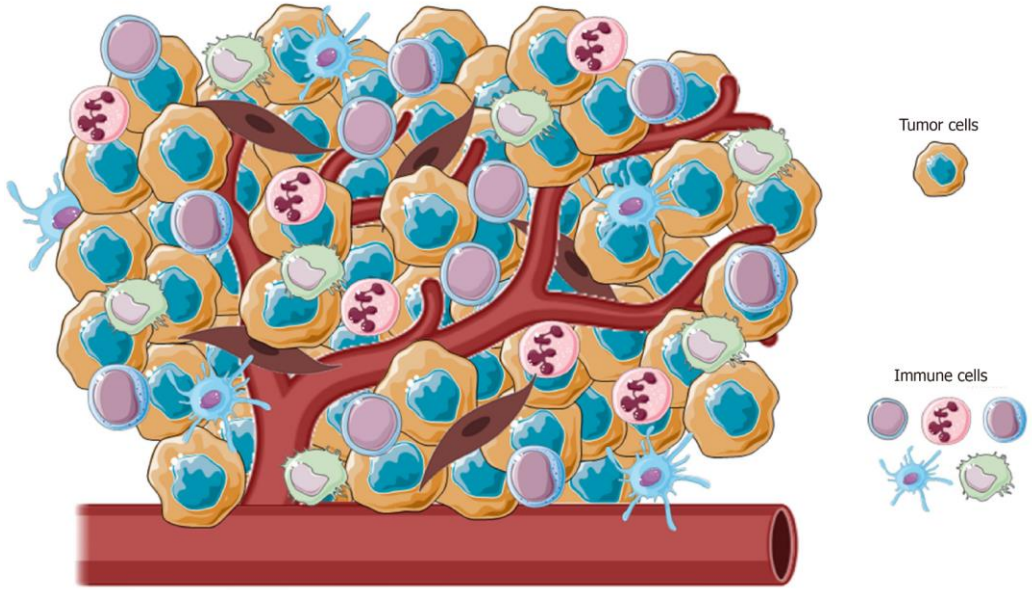
The Tumor Microenvironment (TME)

It’s complicated

Three dimensional

Dynamic

Local effect of cells, stroma, cytokines, vessels, metabolism, etc



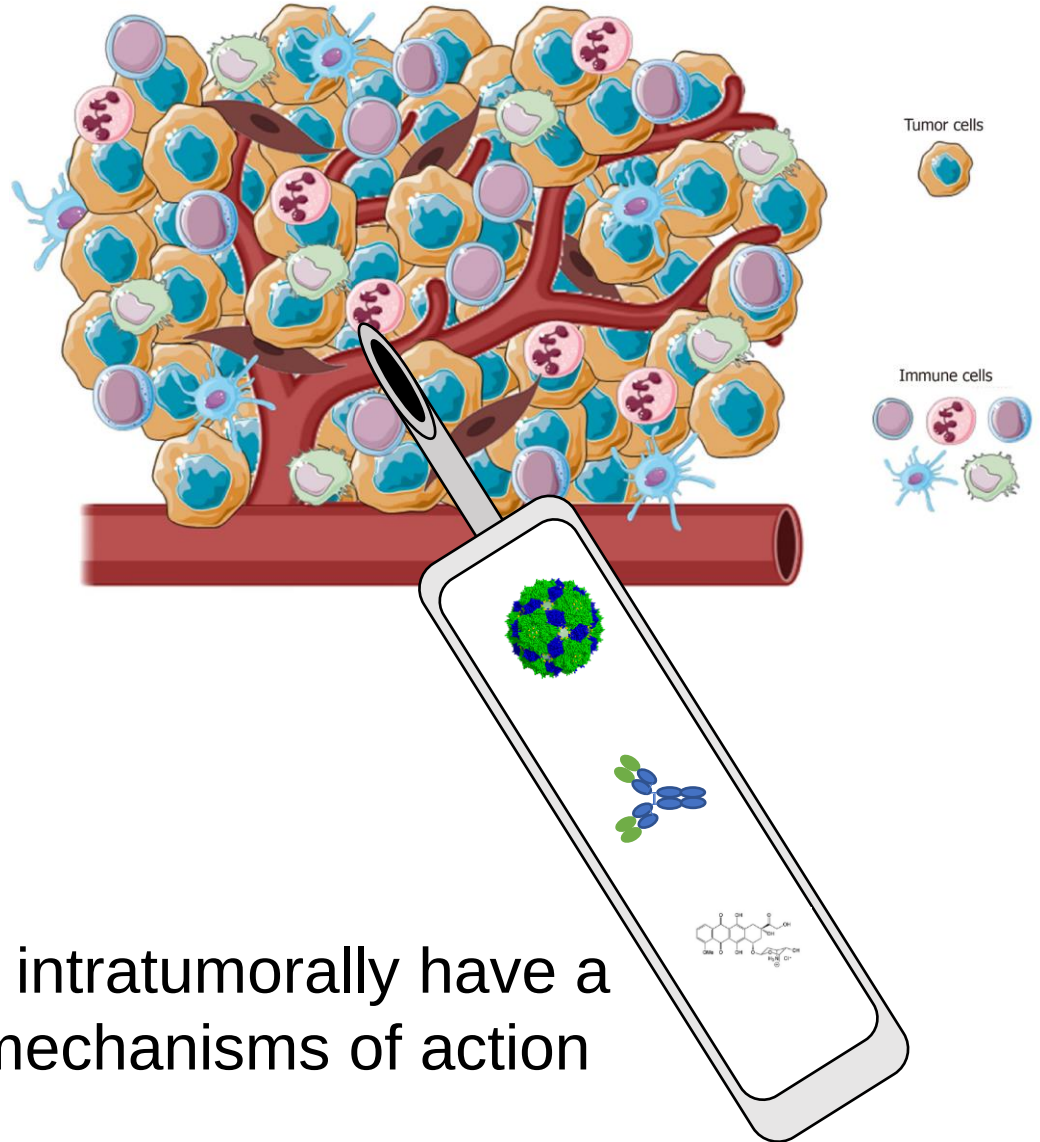
In vitro studies hours – days

In vivo efficacy weeks – months

In situ immunization

Regulatory issues related to intratumoral therapy

Not extensively defined

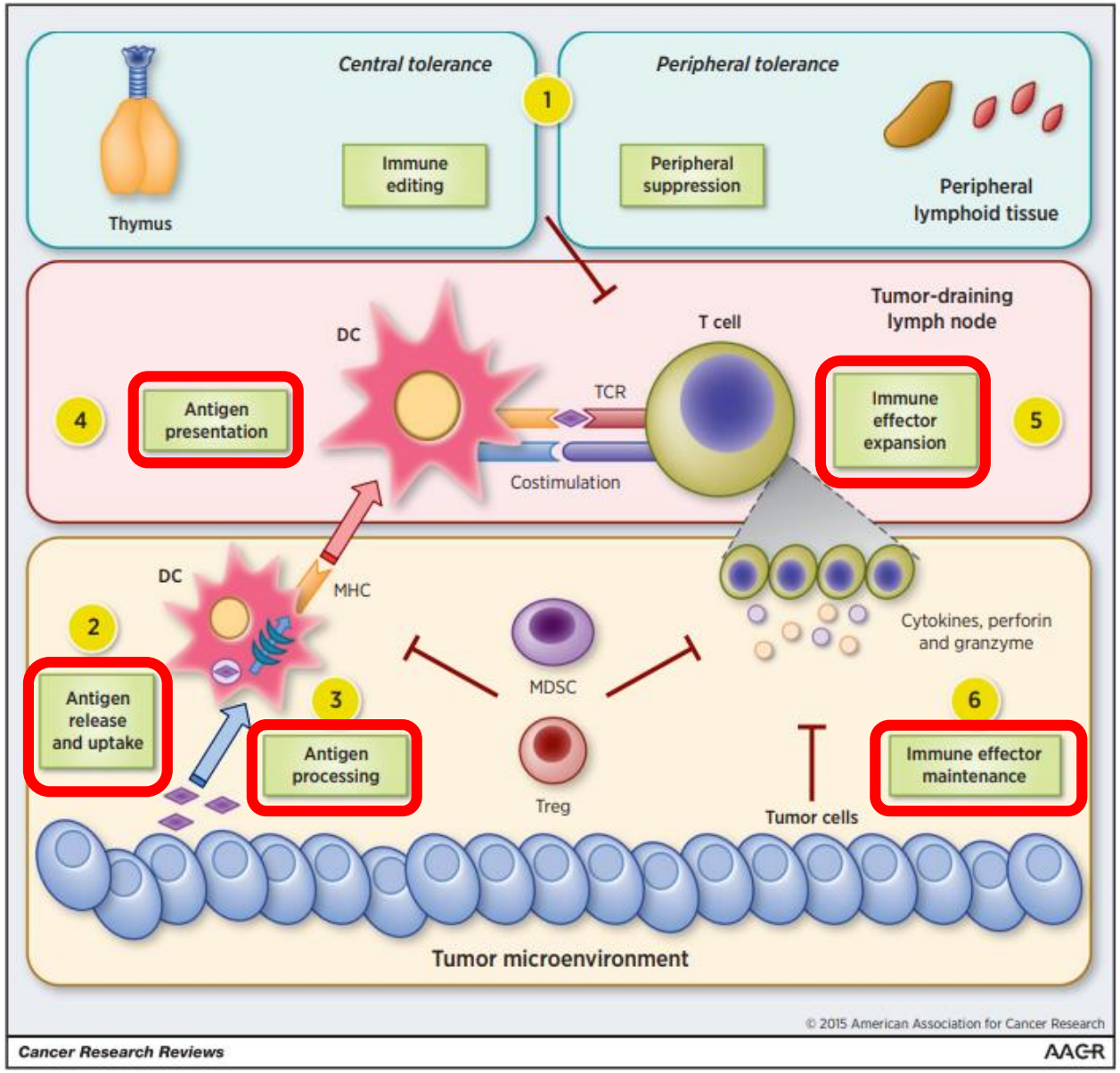


Therapeutics injected intratumorally have a variety of proposed mechanisms of action

Aspects of intralesional therapy with regulatory impact

- Mechanism of action
- Dosing, pharmacokinetics and pharmacodynamics
- Injection procedure
- Safety and toxicity
- Local and systemic response
- Changes over time
- Combination therapy

Changes in the TME following intralesional therapy that contribute to breaking immune tolerance



Makkouk and Weiner, 2015

Mechanisms of action

Small molecules, viruses, virus-like-particles, other biologics

- Impact on various aspects of the immune response
- Infectious versus non-infectious agents

Enhancing the immune response

- Antigen release
- Antigen uptake
- Antigen processing and presentation
- Development of a T cell response
- Maintenance of the T cell response

Dosing, Pharmacokinetics and Pharmacodynamics

Dose
- Fixed
- Based on body size
- Based on size of injected tumor

Injected volume
- Fixed
- Based on body size
- Based on size of injected tumor

Diluent

Pharmacokinetics
- Systemic drug levels
- Intratumoral drug levels

Pharmacodynamics
- Local biologic impact
- Systemic biologic impact
- Surrogate biomarkers

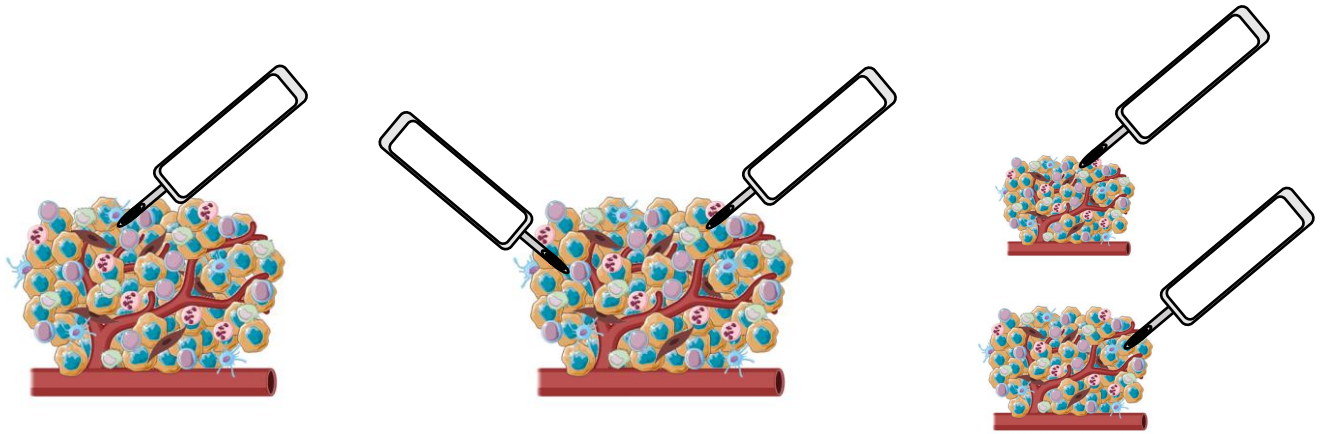
Injection Procedure

Who performs injection

- Clinical oncologist
- Surgeon
- Interventional radiologist
- Training and certification

Distribution of dose

- Single lesion, single injection
- Single lesion, multiple injections
- Multiple lesions



Documenting injection procedure

- Lesions injected
- Distribution of overall dose within a lesion or in multiple lesions

Toxicity and Safety

Toxicity

- Grading local reaction
- Systemic toxicity (e.g. cytokine release syndrome)
- Determining MTD or OBD

Safety issues for potentially infectious agents

e.g. talimogene laherparepvec (T-VEC)

- Patient and environmental safety issues addressed in part by attenuation of HSV
  - Disseminated HSV is rare
  - Viral shedding is rare - No cases of transmission of the oncolytic virus have been reported
- Contact infection control policies
- Post market evaluation

Local and systemic response

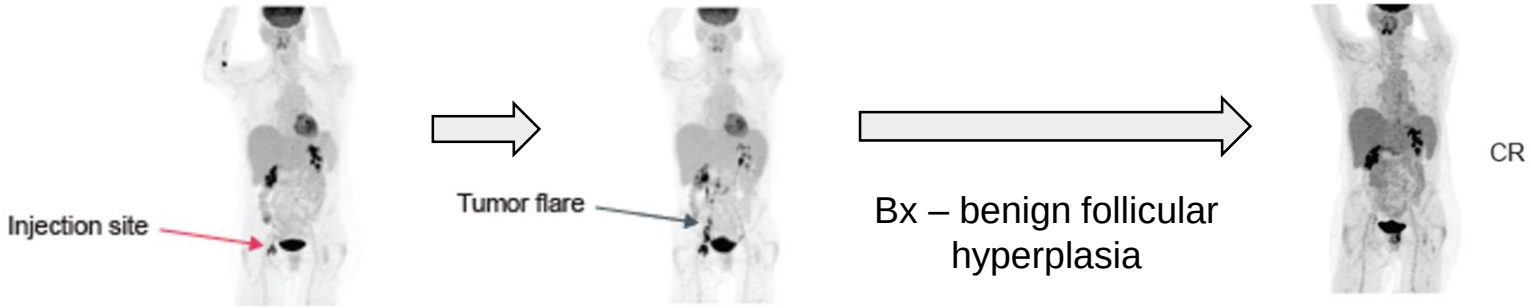
Nature of response

- Impact of injection procedure itself independent of therapeutic agent
- Response of non-injected lesions as indication of systemic response
- Identification of index lesions that are not injected to assess systemic therapeutic response
- Mixed responses

Distinguishing residual tumor from benign lymphoid hyperplasia radiologically

- Flare reaction on PET

Lymphoma trial of in situ immunization with Vidutolimod, a virus like particle containing a TLR9 agonist



Assessing response to neoadjuvant therapy after injection of primary lesion

- Response of primary lesion
- Pathology of resected lesion or draining nodes
- Rate of recurrence

Changes over time

Immune response evolves over time

- Can multiple injections lead to an immunosuppressive TME?
- Planning number of injections
- Time between injections
- Sample tumor microenvironment since needle is in the tumor anyway

Stopping therapy

- Predetermined number of injections
- Discontinue therapy when interventionalist no longer able to access tumor
- Radiologic or pathologic confirmation of response

Combination therapy

Choosing the right combination

- *In vitro* data
- Animal model data
- Correlative science

Systemic versus intralesional

- Inject together or separately

Sequencing of therapy

- Based on proposed mechanism of action

Conclusion

Intralesional therapy designed to enhance the anti-tumor immune response carries with it a unique set of regulatory issues

Development of guidelines to address these issues in a consistent manner will be valuable as additional agents designed for intralesional therapy are developed and combinations emerge