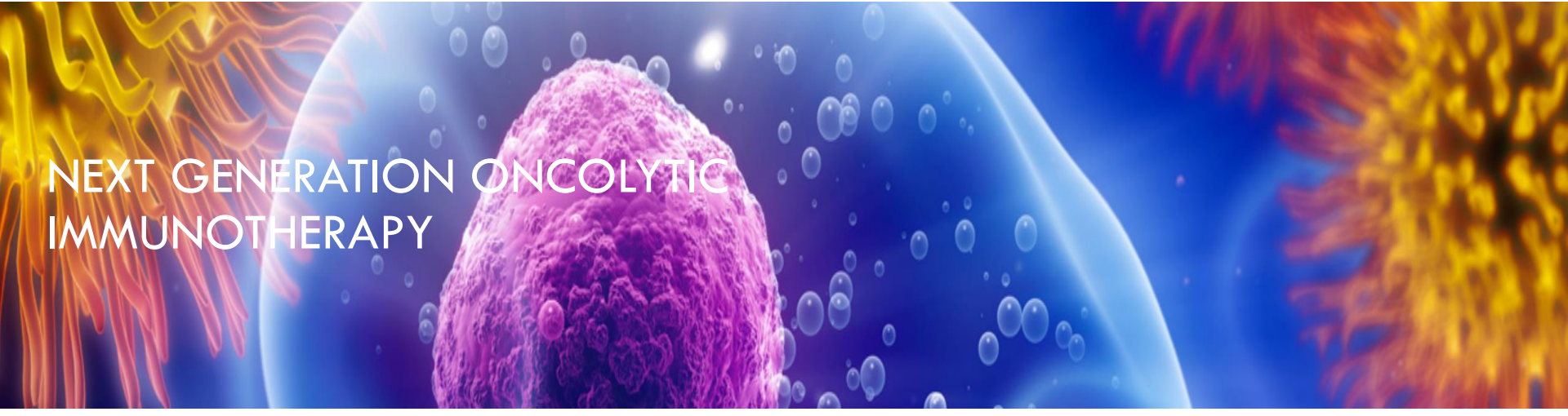
Replimune®



CHI Immuno-oncology Summit Boston

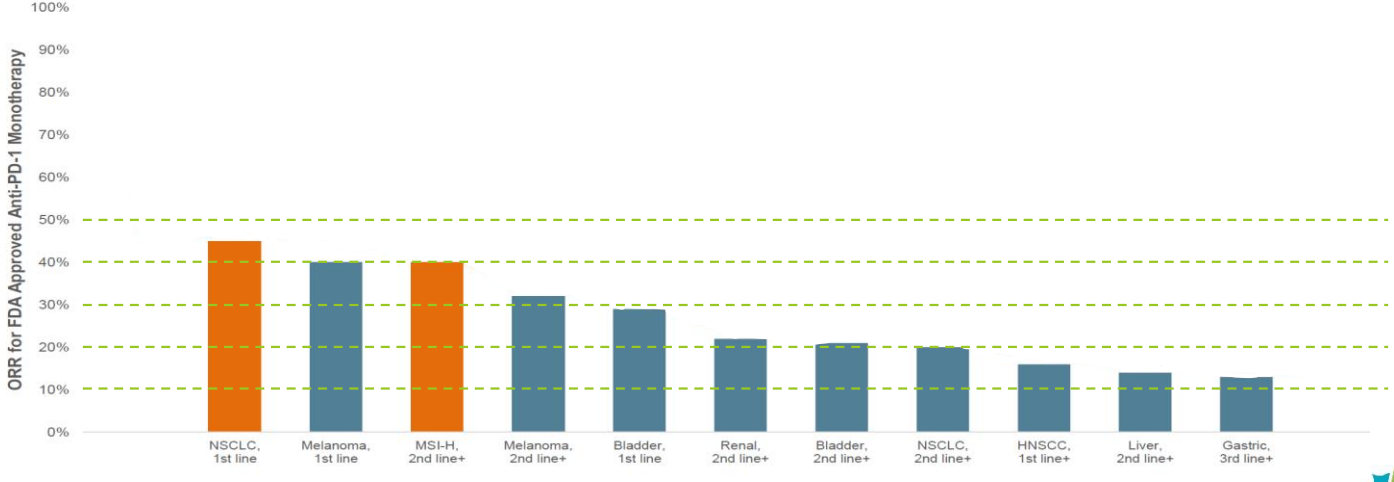
27th August 2018

Safe harbor

Any statements contained herein that are not statements of historical facts may be deemed to be forward-looking statements which are subject to risks and uncertainties. Accordingly, actual outcomes or results may differ materially from those indicated in these statements for many reasons, including, without limitation, risks associated with our collaborations, our clinical development activities, regulatory oversight, as well as the risks, uncertainties and other factors described under the heading "Risk Factors" in our registration statement filed on Form S-1 (including a prospectus) with the SEC which was declared effective on July 19, 2018. Our forward-looking statements are based on beliefs, assumptions and information available to the Company only as of the date of this presentation and include, but are not limited to, statements regarding the development of our product candidates, the success of our collaborations, and/or the delay or lack of success of any of our ongoing or planned clinical trials. We undertake no obligation to publicaly update such forward-looking statements to reflect subsequent events or circumstances.

The problem

- Immune checkpoint blockade is only effective for patients with a pre-existing immune response to their cancer and whose tumors are inflamed
- The key problem to be addressed in immuno-oncology is how to most effectively vaccinate patients against their own tumor for the rest
  - 'The rest' represents the vast majority of cancer patients



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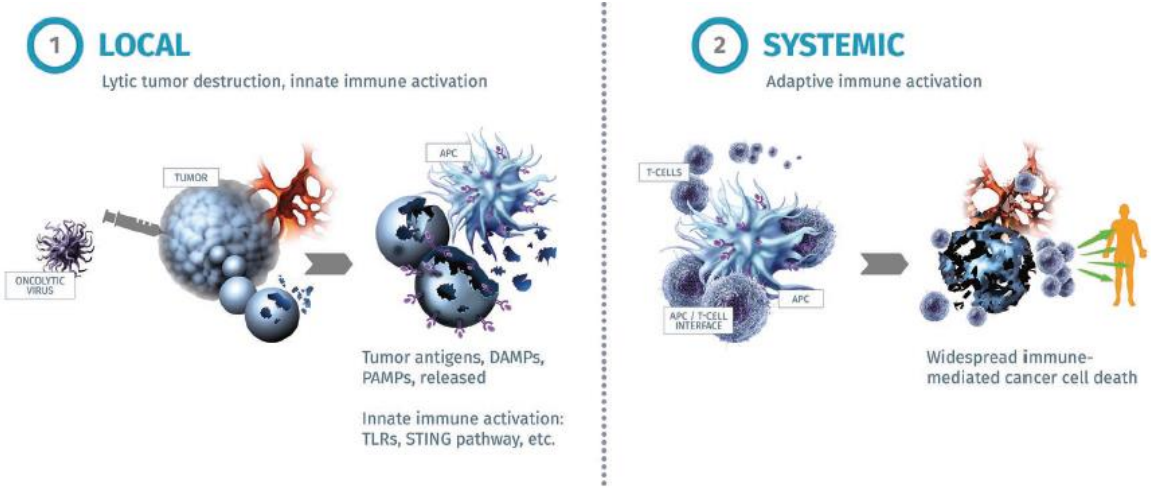
Objectives

- Render all solid tumor patients responsive to immune checkpoint blockade
  - Immunologically cold tumor types & patients, as well as immunologically hot
- Maximally vaccinate patients against their own cancer
  - Includes neoantigens, as well as defined antigens
  - Off the shelf approach, no patient specific information or manufacturing
  - Potently activate both innate & adaptive immunity
  - Potentially applicable to all solid tumor patients in combination with anti-PD1/L1

Oncolytic immunotherapy

- The use of viruses that selectively replicate in & kill tumors to treat cancer
  - ✓ Highly inflammatory
  - ✓ Activates both innate and adaptive immunity
  - ✓ Releases the full array of tumor antigens into an inflamed environment
  - ✓ Systemically activates the immune system against the tumor & neo-antigens released
  - ✓ Can be 'armed' with additional genes to increase efficacy
- Single agent T-Vec is FDA approved for the treatment of advanced melanoma



Replimune®

Oncolytic immunotherapy + checkpoint blockade

Oncolytic and immune-based efficacy in its own right

Patient-specific neo-antigen vaccine generated *in situ*

Without a pre-existing neoantigen response, nothing to remove the brakes from

Only some patients respond

Oncolytic immunotherapy is potentially ideal for combination with checkpoint blockade

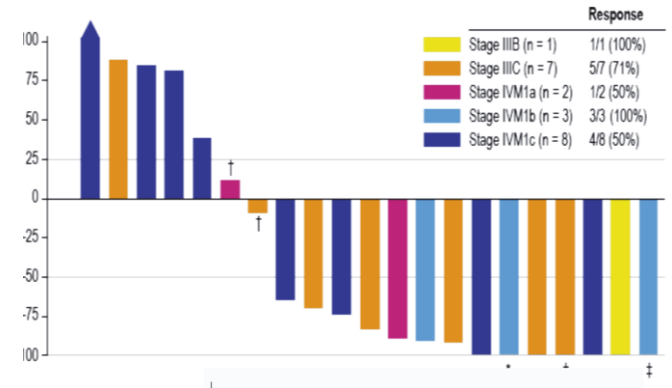
Replimune®

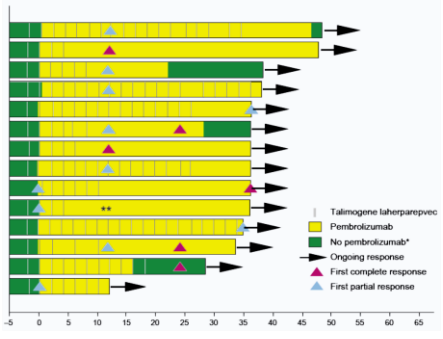
Oncolytic immunotherapy is synergistic with checkpoint blockade

- T-VEC, Cavatak & HF10 are all synergistic, with no added toxicity

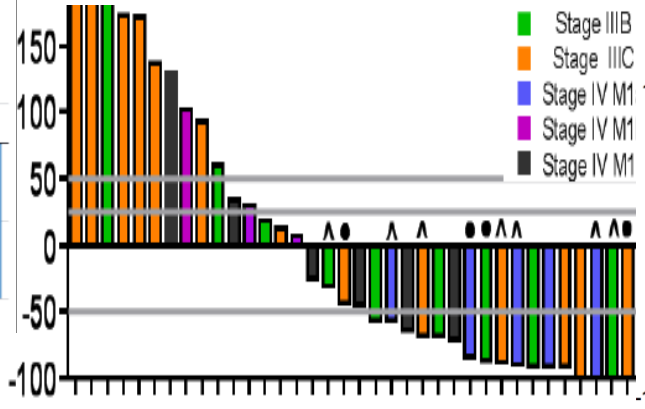
T-VEC+pembrolizumab

Ribas *et al* Cell 2017 170: 1109-1119

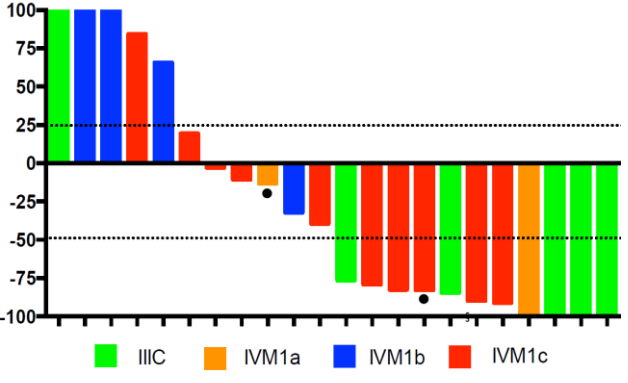




HF10+ipilimumab ASCO 2016



Cavatak+ipilimumab ASCO 2017



Oncolytic immunotherapy turns cold tumors hot

T-VEC+pembrolizumab

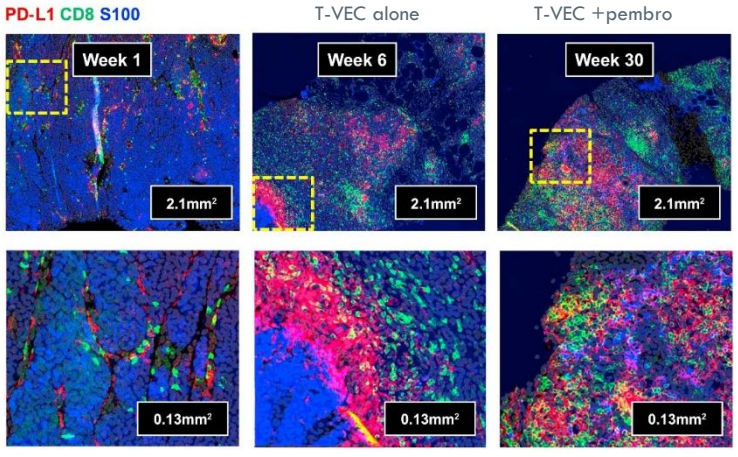
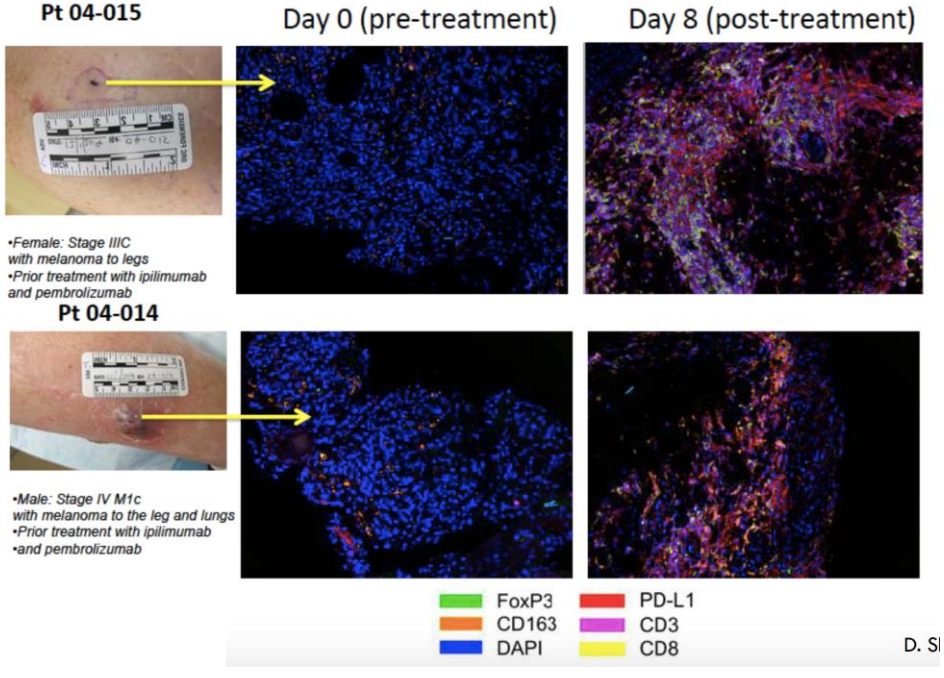


Figure 2. Combination of Talimogene Laherparepvec and Pembrolizumab Is Effective in Patients with Low Tumor CD8⁺ Density
(A) Baseline CD8⁺ density in tumor biopsies according to response rate. Magnitude of bars indicates baseline tumor CD8⁺ density in each patient's baseline biopsy, and best overall response is indicated on x axis and by bar color. Gold, CR; pink, PR; blue, PD.
(B) Baseline PD-L1 by IHC status (1% cutoff) and IFN-γ signature score by NanoString analysis is shown under each patient's CD8 result. Best overall response per investigator is shown as of cutoff date of August 2016. Abbreviations: CR, complete response; IFN-γ, interferon γ; IHC, immunohistochemistry; NA, result not available; PD, progressive disease; PR, partial response.

Ribas *et al* Cell 2017 170: 1109-1119

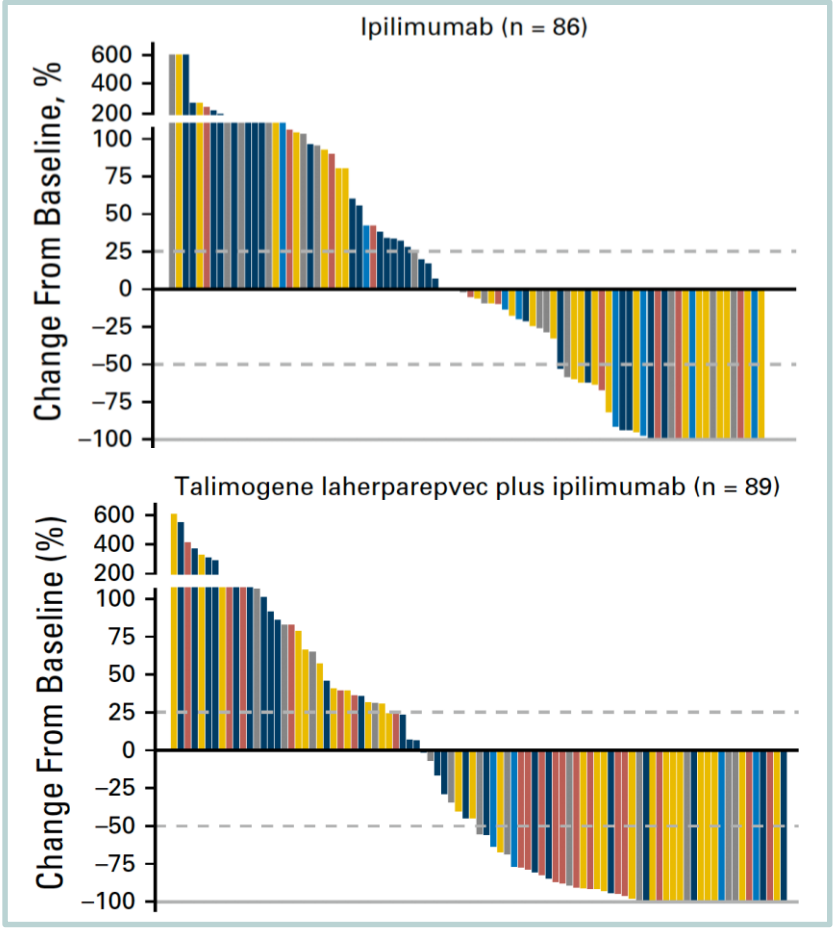
Cavatak



Viralytics SITC presentation 2017

Compelling controlled phase 2 data: T-VEC + ipilimumab

- T-VEC + ipilimumab vs. ipilimumab alone Stage IIIb-IVM1c melanoma
- Response rates (N=198) more than doubled with T-VEC + ipilimumab vs. ipilimumab alone (38% vs. 18%)
- For visceral lesions (none injected), the response rate was 35% for T-VEC +ipilimumab vs. 14% for ipilimumab alone
- No additional toxicity as compared to ipilumumab alone



Chesney et al JCO, 2017

‘Next generation’ oncolytic immunotherapy objectives

- Extend the utility of oncolytic immunotherapy beyond melanoma to all solid tumor types by
  - Maximizing local tumor destruction, immunogenic cell death & antigen release
  - Maximizing systemic immune stimulation
  - Expression of transgenes that enhance ICD and/or induction of host immunity
    - “Oncolytic immuno-gene therapy”
- Generate the ‘ultimate’ universal tumor specific neo-antigen vaccine *in situ* in the patient
- Treat all solid tumor patients in combination with up-front anti-PD1/L1

Our Immulytic platform uses HSV

- HSV as an oncolytic agent has ideal properties for cancer immunotherapy:
  - ✓ Biology & disabling mutations well understood
  - ✓ Genetically stable, non-integrating
  - ✓ Improves safety & efficacy, including in combination with checkpoint blockade
  - ✓ Infects human tumor cells broadly, highly lytic & inflammatory, kills mainly by necrosis
  - ✓ Potent activator of innate immunity, including through STING/cGAS & TLRs
  - ✓ Large viral genome with the capacity to package multiple genes
    - These are then delivered and expressed in the tumor and draining lymph nodes – the optimal sites for anti-tumor immune response induction
    - Replimune's product candidates contain 2-4 exogenous genes

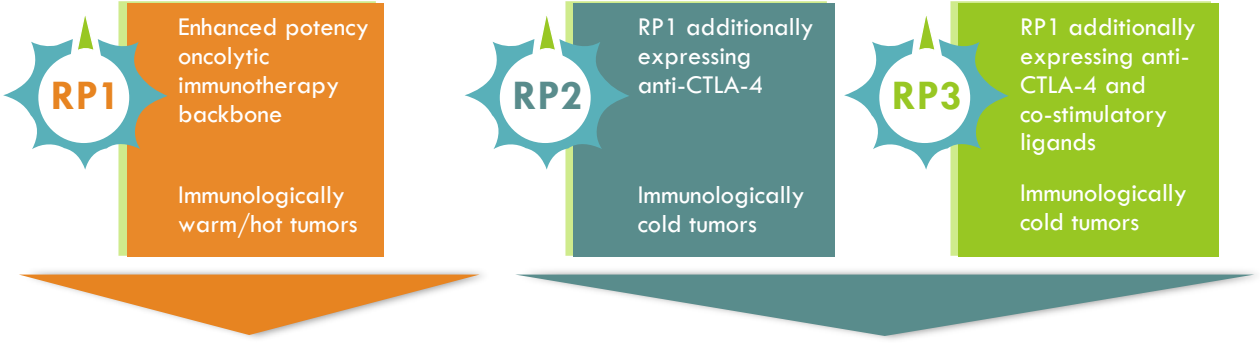
Our Immulytic platform

1. A potent underlying HSV-1 strain

There is great diversity among clinical HSV strains

We tested 29 new strains & selected the most effective

We have armed all of our product candidates with two to four genes encoding therapeutic proteins



2. Increased tumor killing & spread

In addition to the potent cytokine GM-CSF, a modified fusogenic protein (GALV) is expressed

Large bystander effect, highly immunogenic cell death

Provides a substantial increase in direct tumor killing potency

3. Delivery of potent immune stimulatory proteins

Focus on pathways where systemic engagement is sub-optimal

CTLA-4 blockade, immune-costimulatory pathway activation

Delivery directly to the tumor

Replimune®

1. Panning HSV sequence diversity

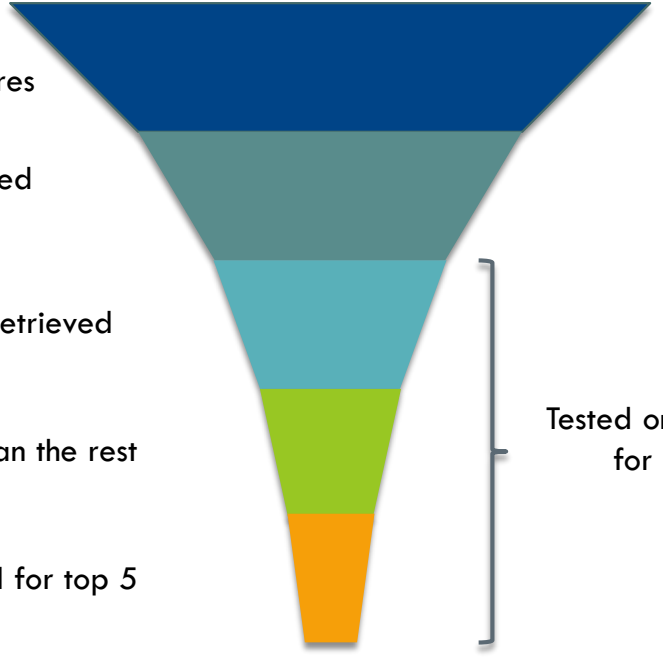
181 volunteers who get cold sores

Swabs from 72 volunteers received (June 2015-Feb 2016)

30 virus isolates retrieved

9 clearly better than the rest

Clear rank order identified for top 5

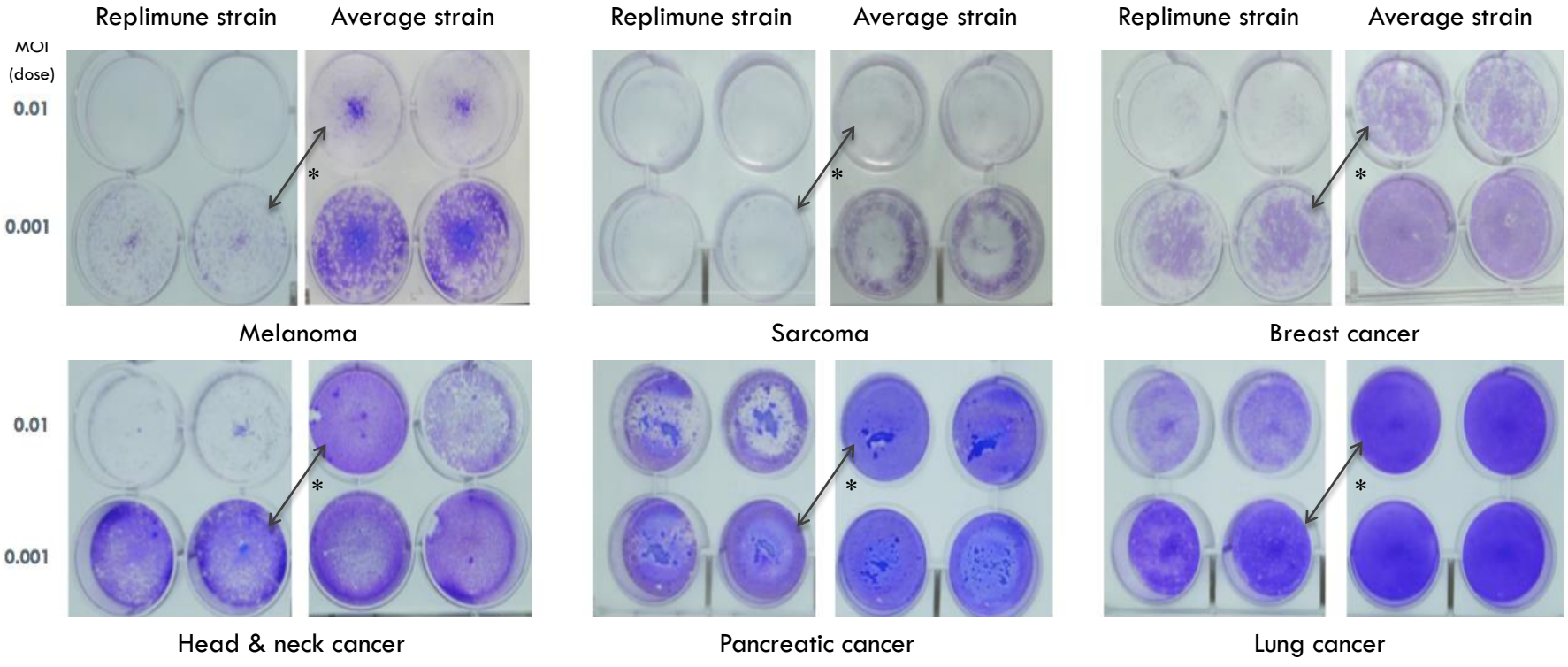


Tested on a panel of human tumor cell lines for killing ability

Best chosen for further development

Replimune®

A high potency underlying HSV strain



Replimune's selected strain is ≈10 fold more potent than an 'average' clinical strain

The 30 strains fell into 3 groups, a middle group, a poorer group and a more potent group

*Replimune's strain requires 10 fold less virus than an average strain to give equal killing

2. Increased tumor cell killing and spread

- A potent fusogenic glycoprotein (GALV-GP *R*-) is expressed to further increase oncolytic potency and spread
- Rapidly kills cells by cell membrane fusion
- Also results in highly immunogenic cell death*
- 10-100 fold improvement in dose response such that
  - Local effects are greatly enhanced through enhanced oncolysis and cell to cell spread
  - Increased levels of tumor antigen are released to enhance the vaccination effect
- Synergy with immune checkpoint blockade would be expected to be increased

*Bateman et al 2000 Cancer Research **60,** 1492
Vile et al 2002 Cancer Research **62,** 6566
Errington et al 2006 Gene Therapy **13,** 138

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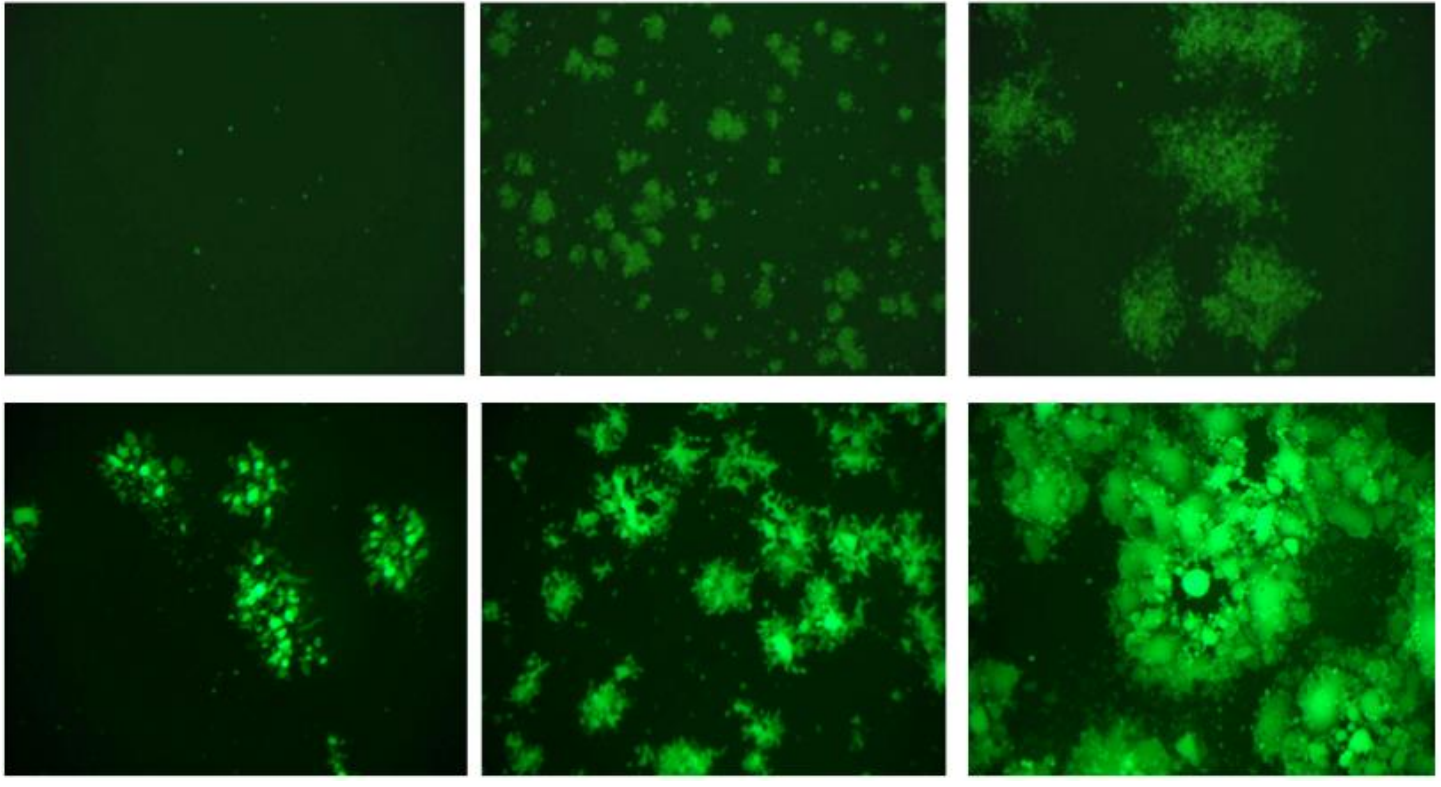
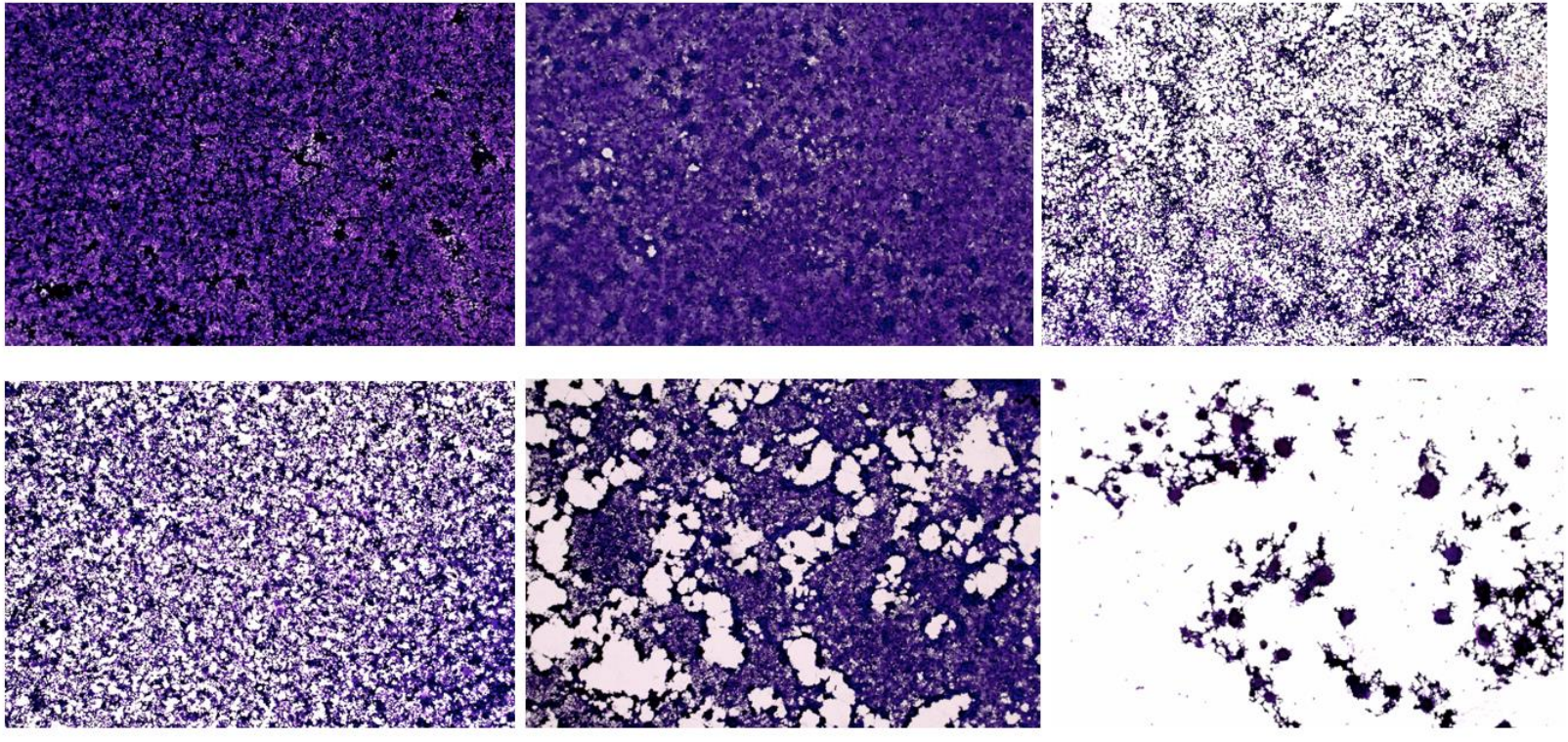
GALV expression enhance potency in vitro



GALV expression enhances potency in human tumor cell lines

Strain 18/ ICP34.5-/GFP

Strain 18/ ICP34.5-/GALV/ GFP



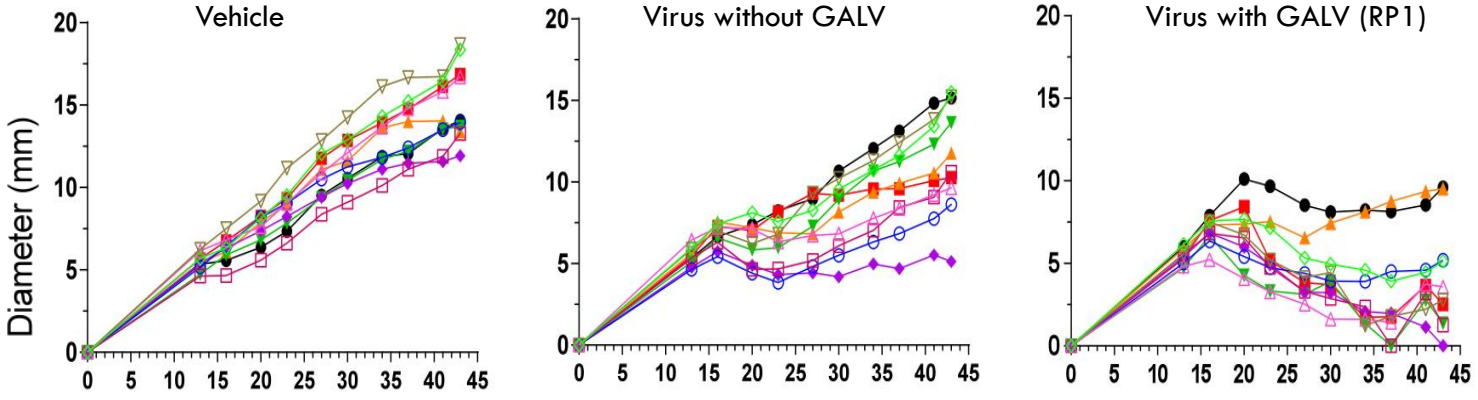
A549 MOI 0.001 48hr | HT29 MOI 0.001 48hr | HT1080 MOI 0.01 24hrs

Cell death assessed by crystal violet staining: low magnification

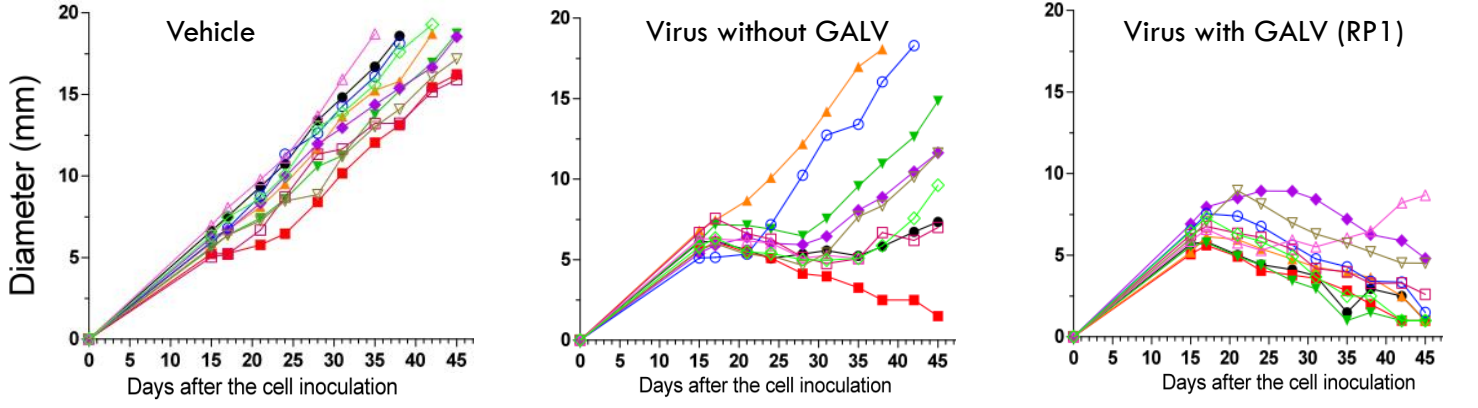
Replimune®

GALV enhances efficacy in vivo

A549
lung cancer



MDA-MB-231
breast cancer



3 injections over 1week; virus dose $5x10^3$ pfu

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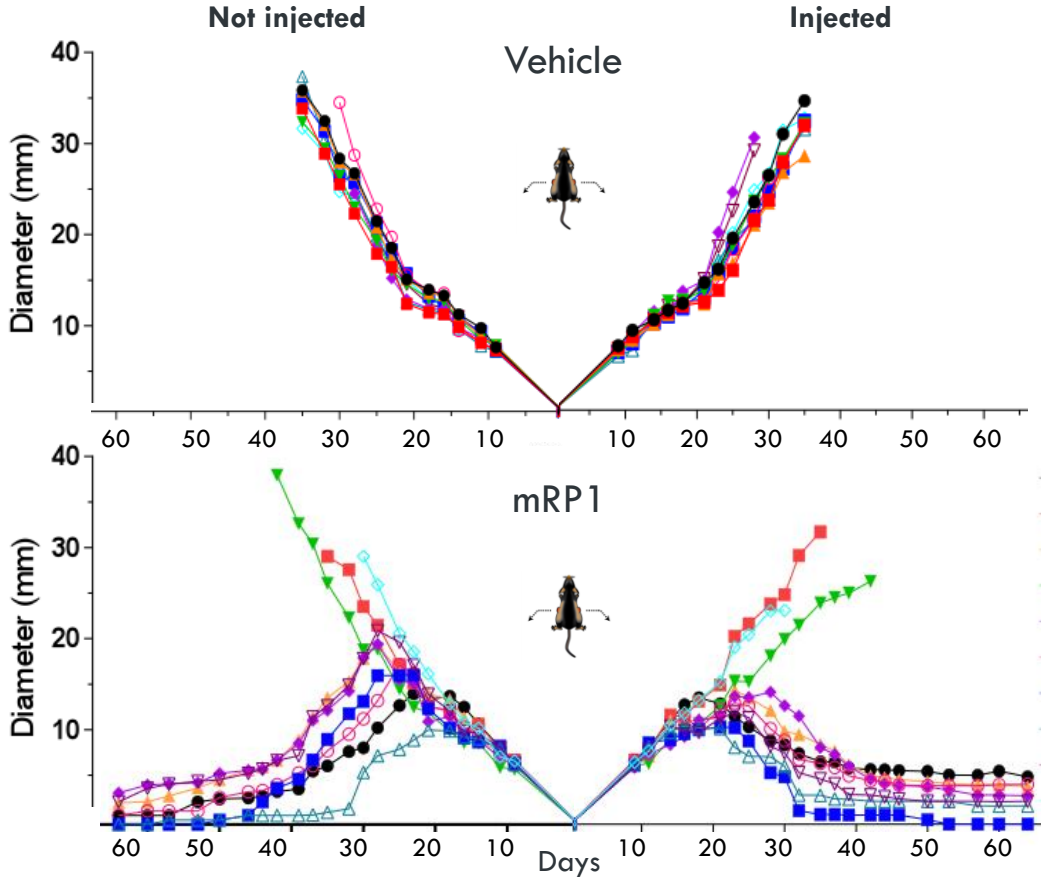
RP1 treats large injected & uninjected tumors

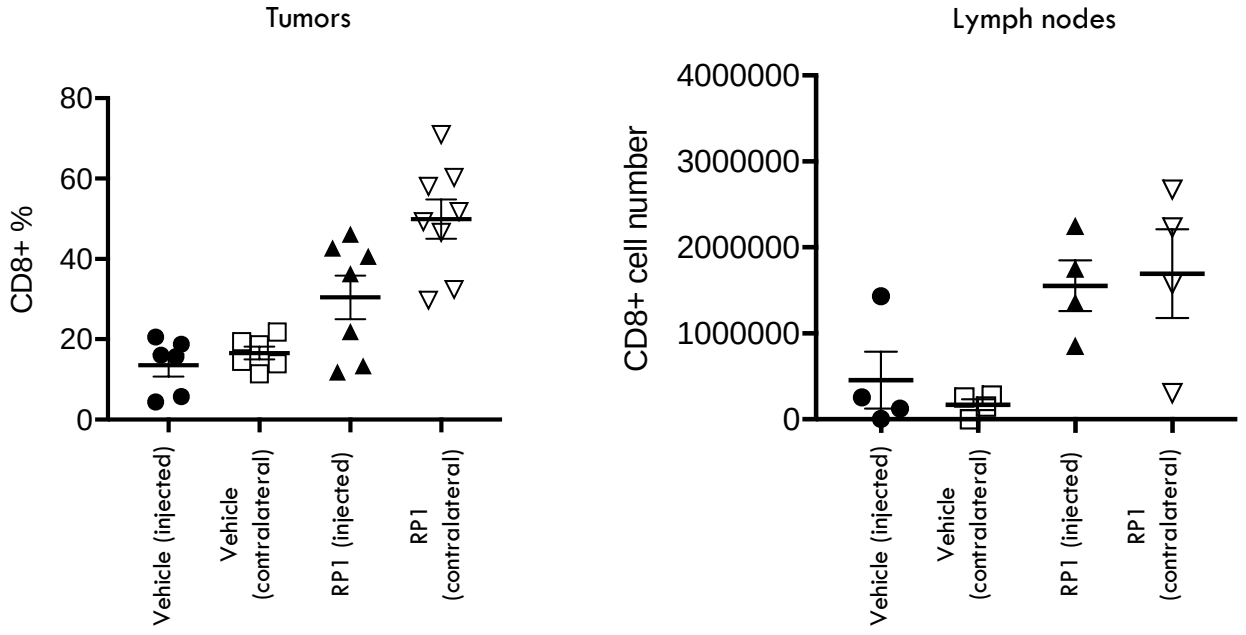


<u>Immune competent rat model (dual flank)</u>

While rat tumor cells are of limited susceptibility to HSV, GALV is active in rats. Right flank tumors injected 5x with $5x10^6$ pfu

Replimune®

CD8+ T cells are increased in tumors and lymph nodes



Mouse 4434 melanoma tumors (dual flank)

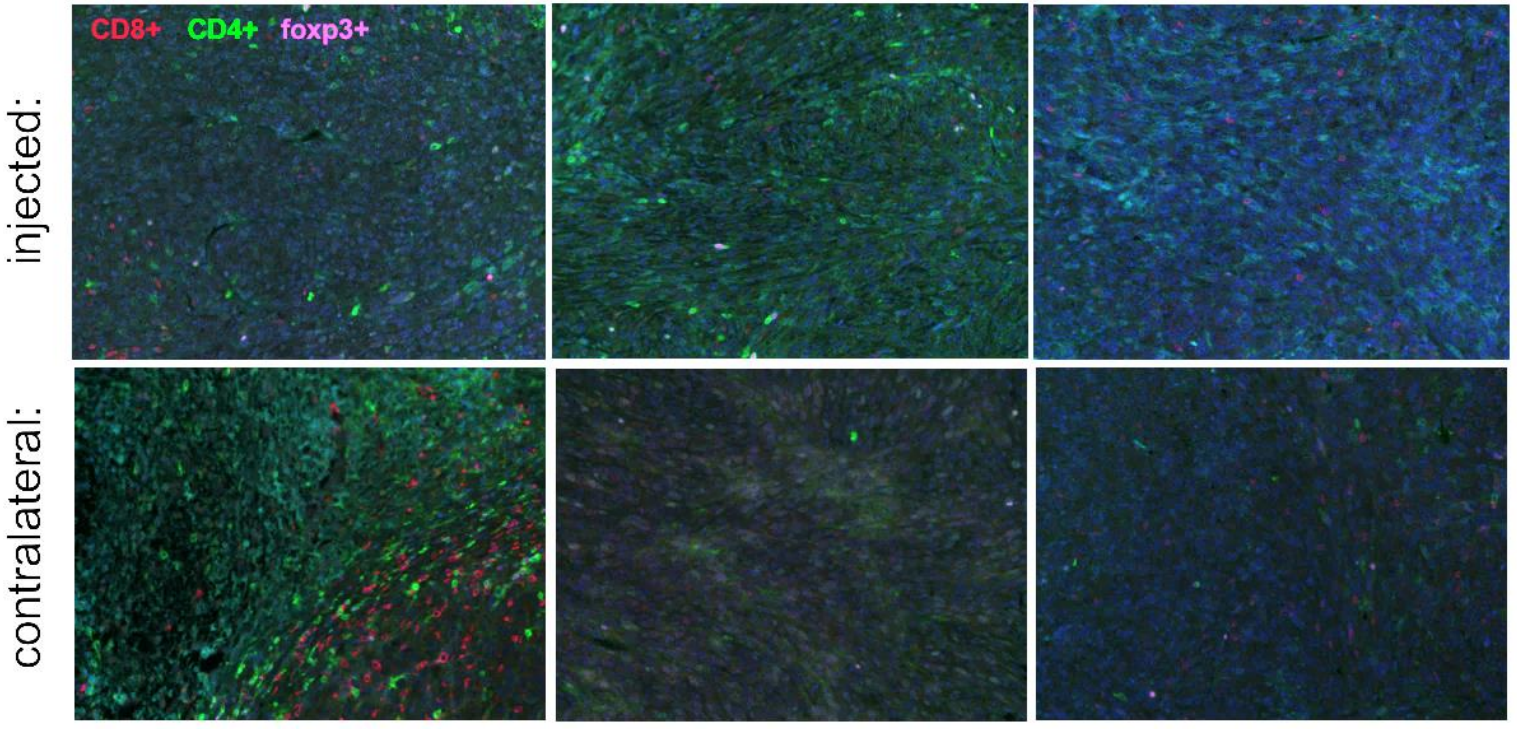
50ul ($1x10^8$ pfu/ml) of RP1 injected 3x into the right tumor only (Days 1, 3, 5)

Tumors & draining lymph nodes were harvested eight days after treatment initiation

Replimune®

Collaboration with The Institute of Cancer Research, London

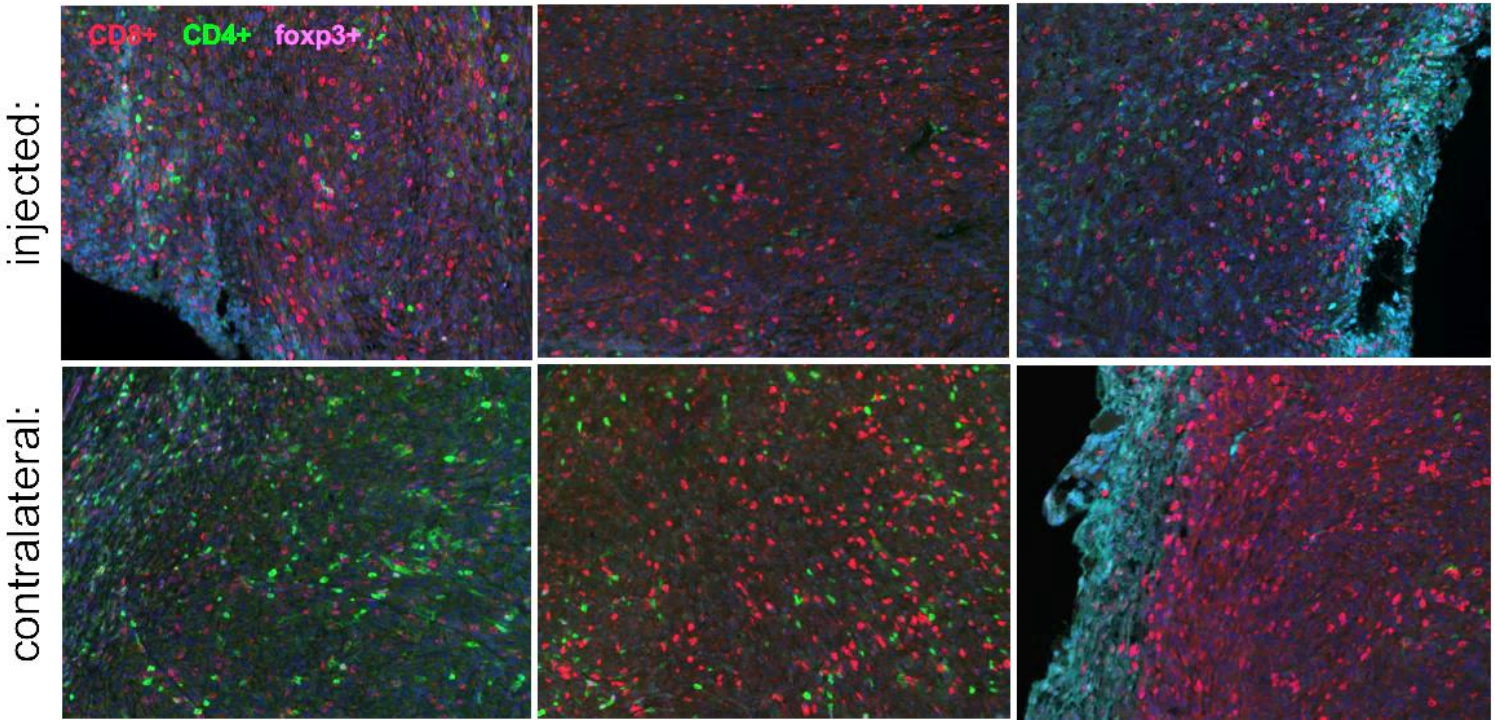
RP1 increases CD8 T cells in injected and uninjected tumors



Representative images 1 per mouse, n=3.

Vehicle

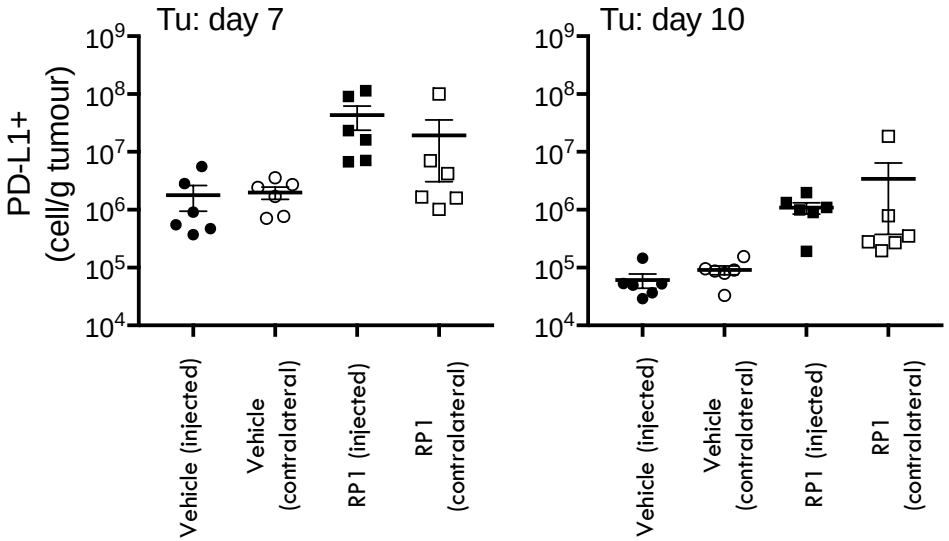
RP1 increases CD8 T cells in injected and uninjected tumors



Representative images 1 per mouse, n=3.

RP1

RP1 increases PDL1 staining in injected and uninjected tumors



Mouse 4434 melanoma tumors (dual flank)

50ul ($1x10^8$ pfu/ml) of RP1 injected 3x into the right tumor only (Days 1, 3, 5)

Tumors were harvested on the indicated days after treatment initiation

Replimune®

RP1: Developing for tumor types with underlying sensitivity to anti-PD1

Potential rapid path to initial approval

RP1 clinical strategy

Phase 1 (underway in the U.K.)

Safety confirmation & determination of dose for phase 2, all comers
(N≈30)

Phase 1/2 clinical trial in ≈150 patients

- Single agent RP1
- RP1 + nivolumab*[1]

Phase 2 (initiates H1 2019)

Defined indications
(N≈30 patients per group)

- Melanoma + nivolumab*[2]
- NMSC[3] + nivolumab*[2]
- Bladder cancer + nivolumab*[2]
- MSI-H cancers + nivolumab*[2]

EXPAND PROMISING COHORTS (dependent on data & FDA input)

Randomized, controlled Phase 2 clinical trial in ≈240 patients with CSCC

Initiates H1 2019

- RP1+ cemiplimab vs. cemiplimab alone#[4]

[1] Includes biomarker component to confirm MOA [2] Efficacy to be assessed by ORR, CR rate and biomarker analysis [3] Non-melanoma skin cancers

[4] Full protocol development underway * Under clinical trial collaboration & supply agreement with BMS for the supply of nivolumab

Under clinical trial collaboration agreement with Regeneron; 50:50 sharing of clinical trial costs

(part of a broader collaboration under which clinical trials in additional tumor types may also be conducted)

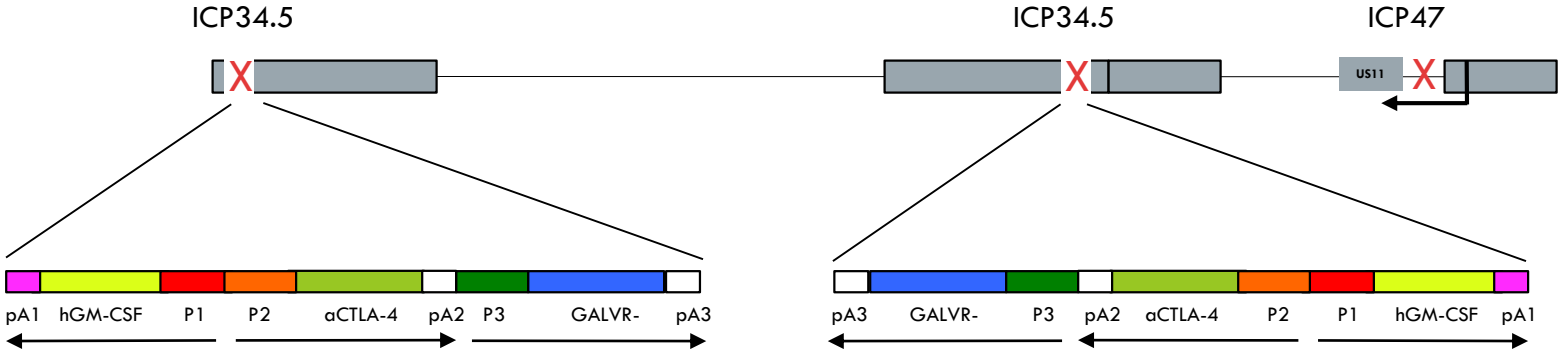
CSCC – potential path to initial approval

- 4,000-9,000 US deaths annually
- No approved therapy
- Anti-PD-1 therapy active
  - Cemiplimab (Regeneron) demonstrated 46% response rate, but low CR rate
  - BLA filed
- Tumors are frequently accessible for direct intra-tumor injection
- We believe CSCC provides the most rapid route to market for RP1
- Registration-directed randomized controlled phase 2 trial in collaboration with Regeneron
  - 240 patients randomized 2:1 (RP1+ cemiplimab vs cemiplimab alone)
  - Primary endpoint ORR, secondary endpoints including CR rate, PFS, OS
  - Intended to initiate H1 2019

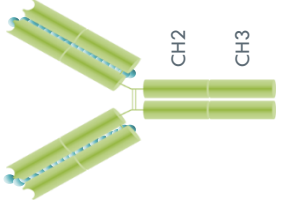
3. Intratumoral anti-CTLA-4 & co-stim agonists

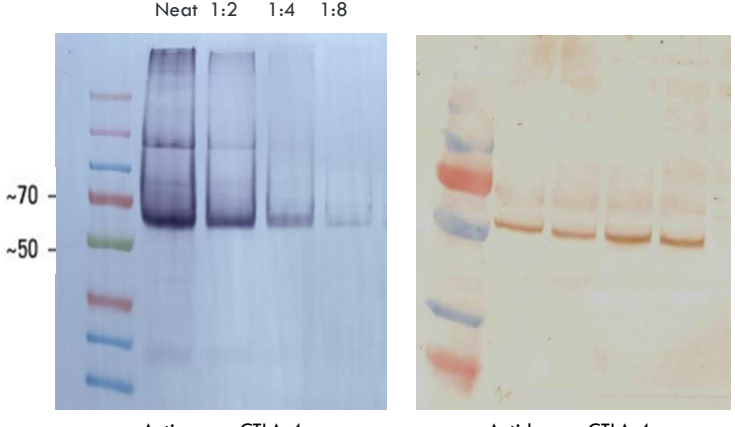
- PD1/L1 & CTLA-4 are the only fully validated IO targets
- Delivery of anti-CTLA-4 directly into the immune response initiating tumor & draining lymph nodes has the potential to be highly effective
  - ✓ Focuses immune potentiation on tumor antigens, reduces systemic toxicity
  - ✓ Blocks Treg activation/inhibition of T cell activation at the site of immune response initiation
- Intratumoral immune co-stimulatory pathway ligands are similarly attractive
  - ✓ Expect activity & toxicity benefits compared to systemic agonist antibodies
- The RP3 series further express pairs of immune co-stimulatory pathway ligands
  - ✓ CD40L, 4-1BBL, GITRL, OX40L, ICOSL
- Expected to further synergize with systemic anti-PD1/L1

RP2 – Immulytic expressing anti-CTLA-4



Anti-mouse or anti-human CTLA-4 constructs are codon optimized secreted scFv molecules linked to mouse or human IgG1 Fc regions





Anti-mouse CTLA-4

Anti-human CTLA-4

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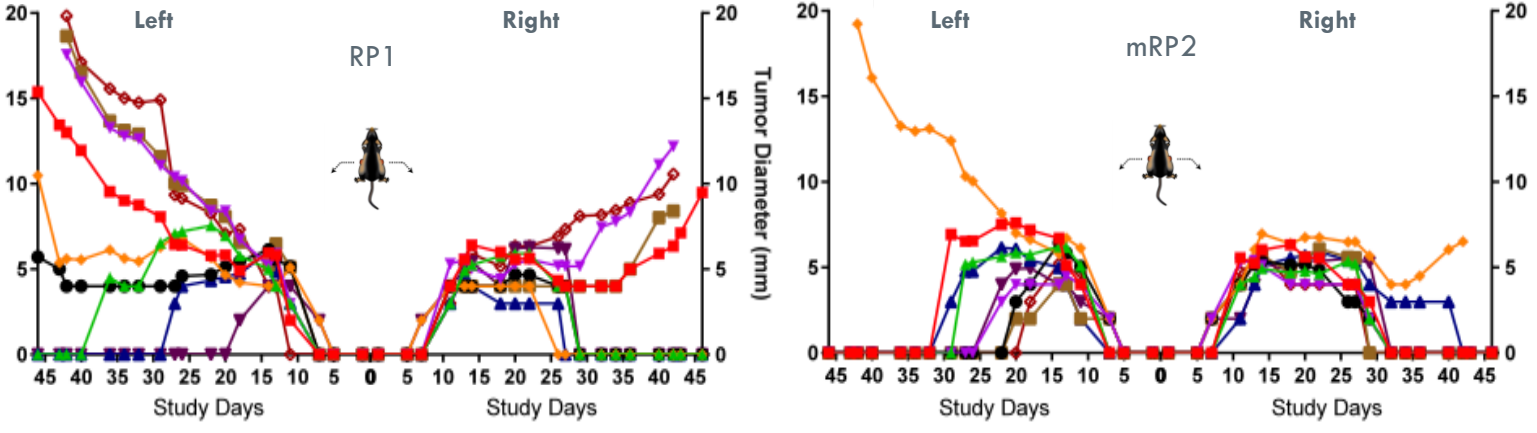
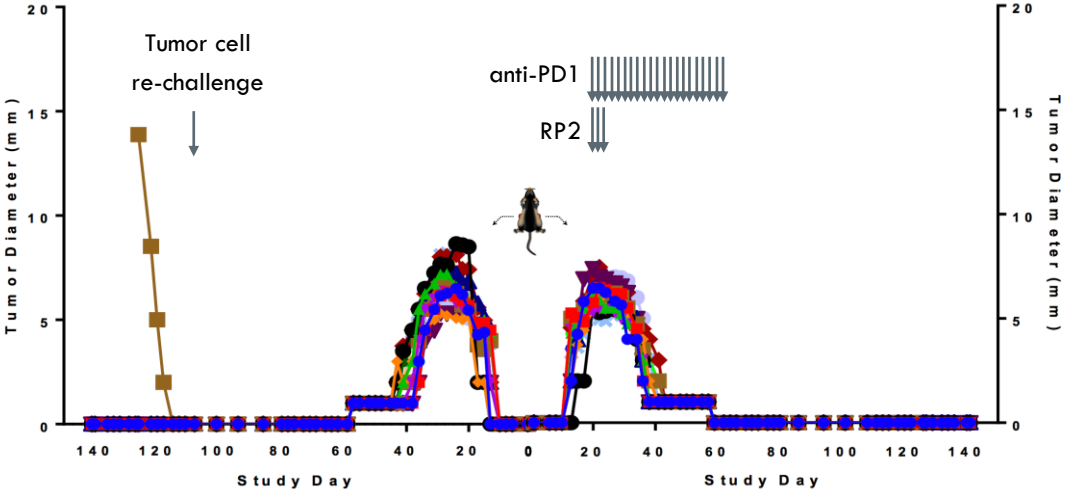
Expression of αmCTLA4 from RP1 enhances efficacy



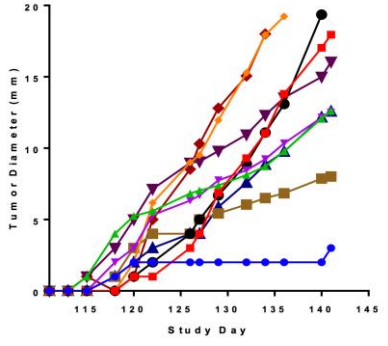
Immune competent A20 mouse tumor model
Subtherapeutic dose for RP1 ($5x10^4$ pfu) injected 3x into the right tumor only

Replimune®

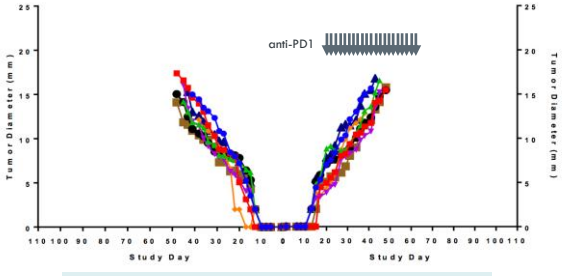
Responses are durable & mice are protected from re-challenge



15 mice previously cured of bilateral tumors by treatment with RP2 + anti-PD1 were re-challenged with tumor cells on the uninjected flank on Day 108 and followed for a further 32 days. Fourteen of the fifteen mice were completely protected from re-challenge.



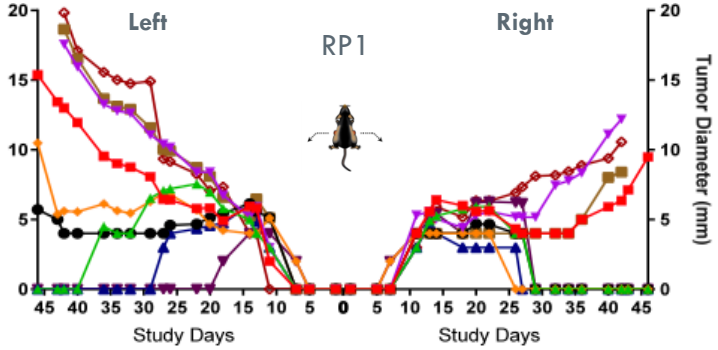
10 tumor & virus naïve mice challenged with tumor cells on the same day all grew tumors



Mice treated with anti-PD1 alone do not respond

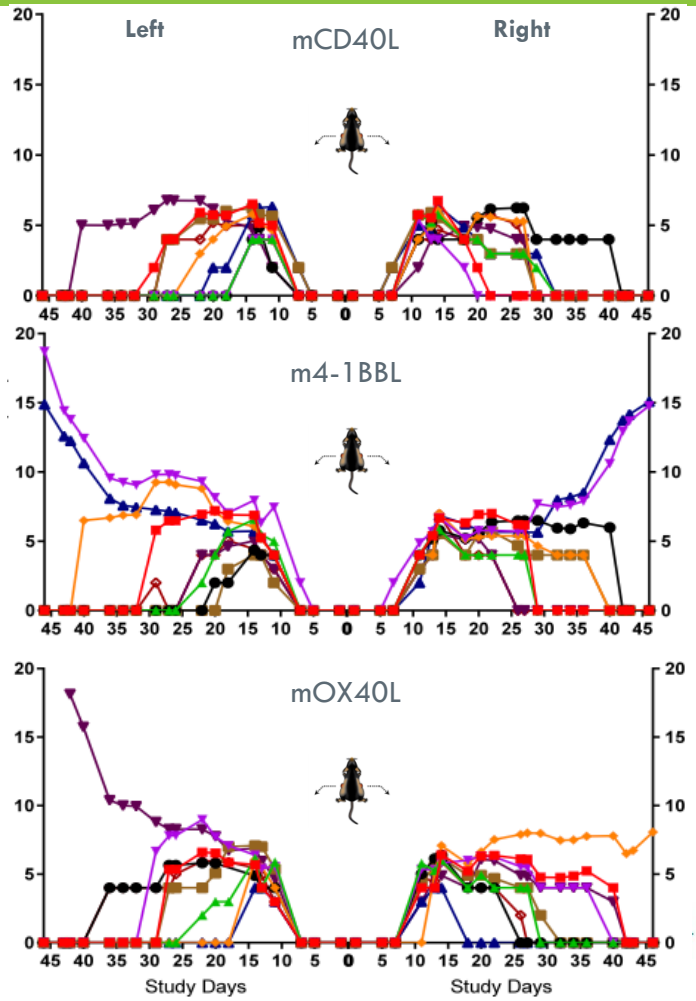
Replimune®

Expression of co-stimulatory ligands from RP1 enhances efficacy



Immune competent A20 mouse tumor model

Subtherapeutic dose for RP1 ($5x10^4$ pfu) injected 3x into the right tumor only



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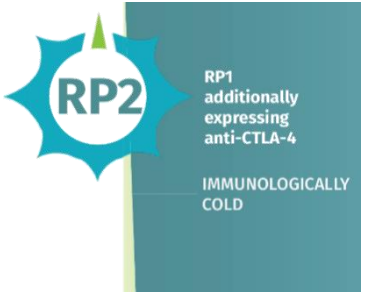
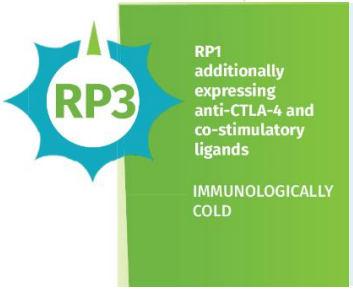
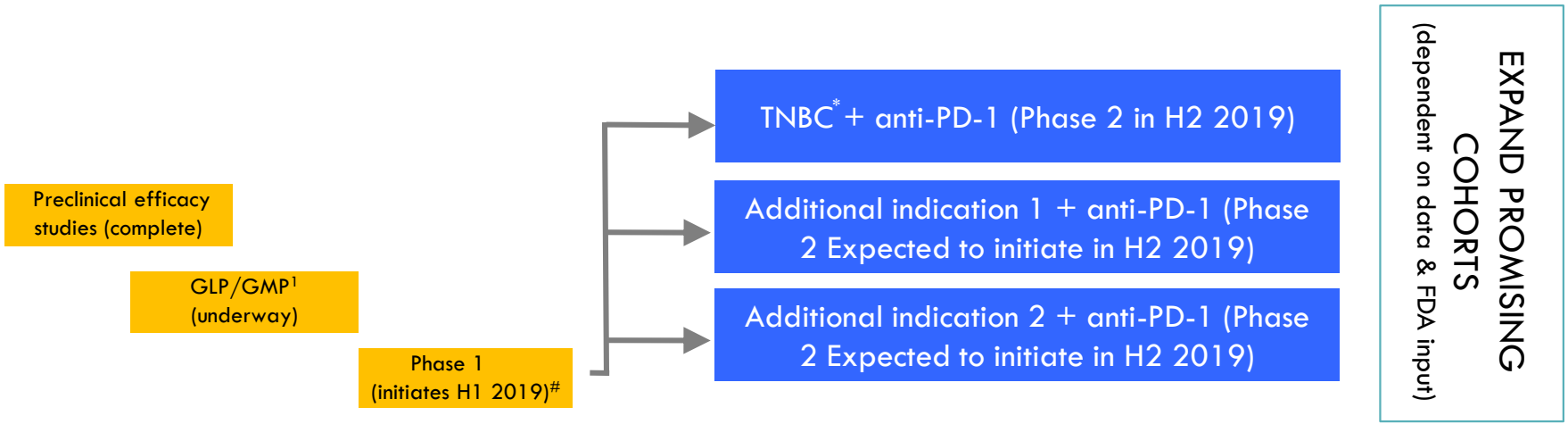




RP2/3: Target anti-PD1/L1 non-responsive tumor types

RP2 current status & clinical strategy



[1] Good Manufacturing Practice

* Triple negative breast cancer

Mixed advanced solid tumors

Critical focus on manufacturing

- Product candidates currently manufactured by a CMO for ongoing clinical development
- For later stage development & commercialization, in-house manufacturing is preferable
- The team has extensive manufacturing experience
- 63,000 ft^2 manufacturing facility recently leased in Framingham, MA, appropriate for multi-product production – intended to include translational biomarker lab
- Expected to be on-line to produce clinical product in H1 2020

*

Replimune®

* Rendered depiction of the intended final facility

Replimune

Fully activating the immune system against cancer

- New HSV-based oncolytic immunotherapy platform
- Armed with 2-4 exogenous genes to increase
  - Direct tumor killing & spread
  - Immune activation
  - "Oncolytic immuno-gene therapy"
- Focus on pathways where systemic engagement may be sub-optimal
- Rapid clinical development of RP1 & RP2 underway/planned
- Commercial scale manufacturing being established
- Aim to become a universal combination partner for anti-PD1/L1 therapies
  - Multi-modal approach
  - Far more practical that competing technologies for providing patient-specific (neoantigen) immune activation
- Potentially applicable to all solid tumors