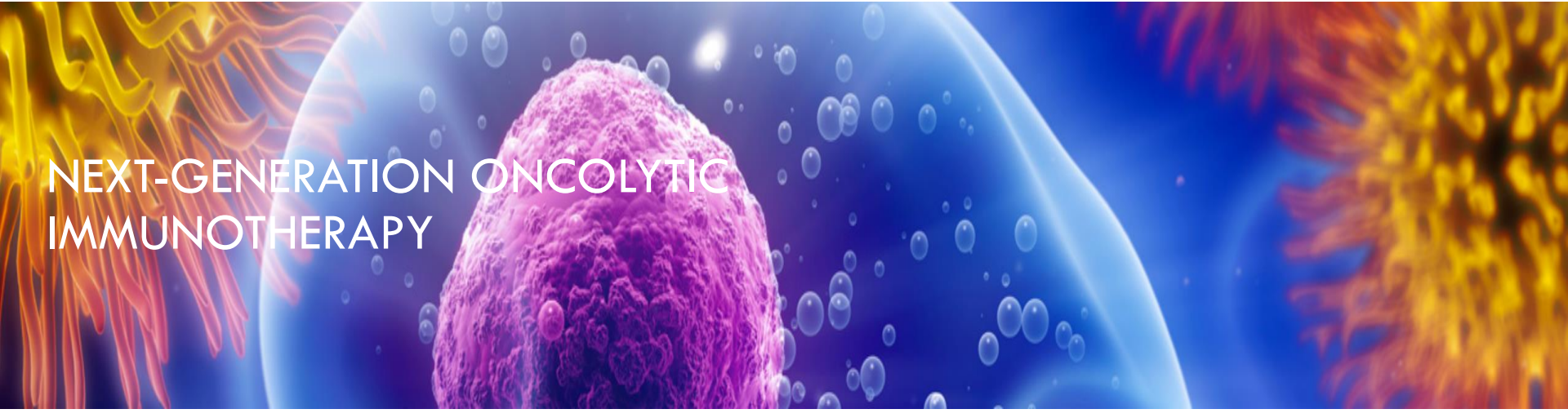
Replimune



37th Annual JPMorgan Healthcare Conference

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 publicly update such forward-looking statements to reflect subsequent events or circumstances.

- Founded in 2015 by the ex-BioVex management team
- Proprietary genetically "armed" oncolytic immunotherapy platform intended to maximally activate the immune system against a patient's cancer
  - "Oncolytic immuno-gene therapy"
- Multiple next generation product candidates armed with 2-4 genes in or being prepared for clinical trials in combination with anti-PD1 therapy
  - Collaboration with BMS for supply of nivolumab (ongoing 150 patient phase 1/2 trial)
  - Collaboration with Regeneron (50:50 cost sharing + cemiplimab supply) across multiple tumor types & products (initially 240 patient randomized controlled phase 2 trial starting H1 2019)
- Commercial scale manufacturing capability being established
- IPO in July 2018 (Nasdaq: REPL); September 30th 2018 cash balance $147.9m
- Headquartered near Boston, MA, labs in the UK, ≈52 employees

The most experienced oncolytic immunotherapy team

ROB COFFIN
Chief Executive Officer
Founder & CTO at BioVex, VP at Amgen

PHILIP ASTLEY-SPARKE
Executive Chairman
CEO BioVex, Chairman at uniQure

COLIN LOVE
Chief Operating Officer
SVP BioVex; VP at Amgen through T-Vec BLA filing

PAMELA ESPOSITO
Chief Business Officer
VP BD at BioVex; CBO at Ra Pharmaceuticals

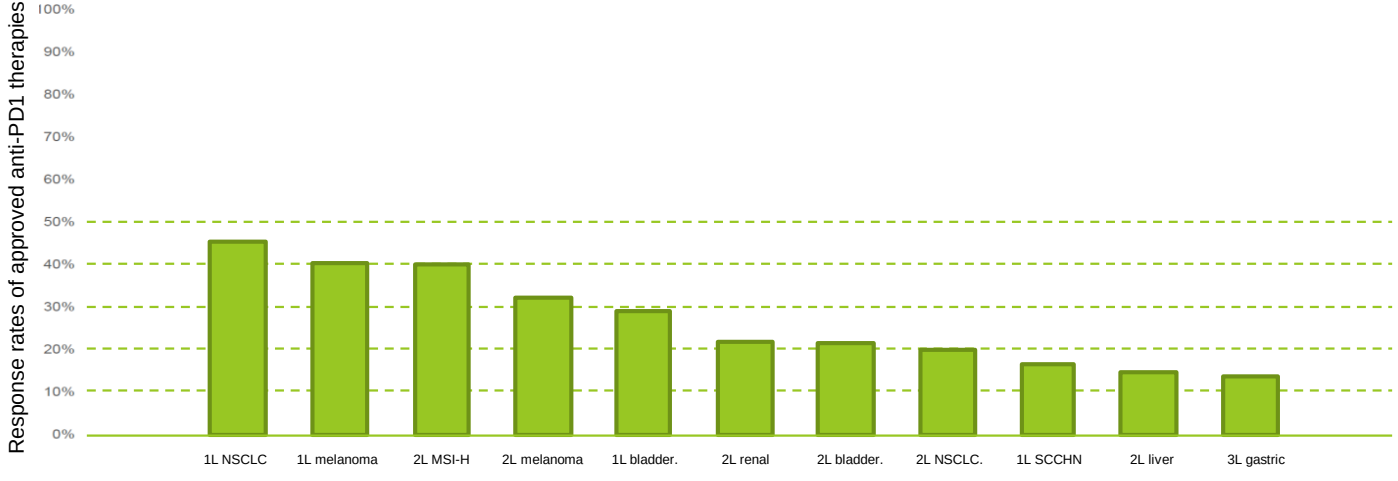
HOWARD KAUFMAN
Chief Medical Officer
World leading clinical immuno-oncologist; ex-SITC President

SUSAN DOLEMAN
VP Clinical Development
Director of Clinical Operations at BioVex/Amgen for T-Vec

ANNE WOODLAND
SVP Regulatory & Quality
VP Regulatory at BioVex; led T-Vec BLA filing for Amgen post acquisition

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

How can we vaccinate?

- Options are limited & mainly not yet proven
  - Vaccines made from cancer cell lines or proteins commonly expressed in cancers
    - Tested in extensively in numerous formats – little evidence of activity
    - *The immunogens are generally recognized as 'self', & therefore not very immunogenic*
  - Vaccines made from immunogens which are uniquely present in a patient's cancer (neoantigens)
    - Arise from the genetic mutations which accumulate in tumors
    - 'Non-self' – should be more immunogenic
    - *Considerable current interest, but not yet clinically proven*
    - *Complex manufacturing – a vaccine needs to be made for each patient following sequencing of their tumor*
  - Activators of the innate immune system
    - TLR9, STING agonists etc - early indications of clinical activity
- Oncolytic immunotherapy – off the shelf, activates innate and adaptive immunity, induces a broad immune response to all antigens present, clinically validated
- Replimune believes this to be the best, most practical & versatile approach

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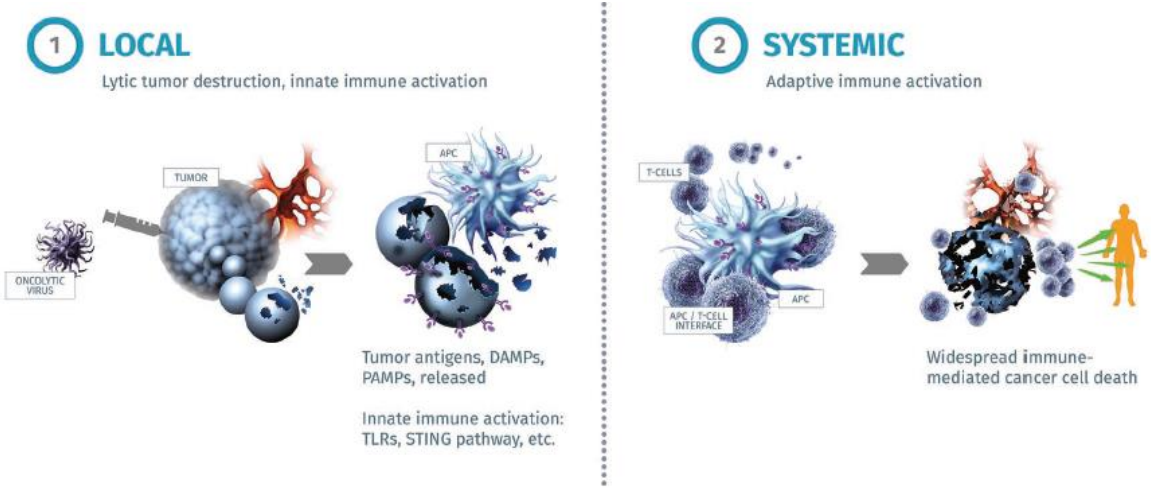
Oncolytic immunotherapy

- 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



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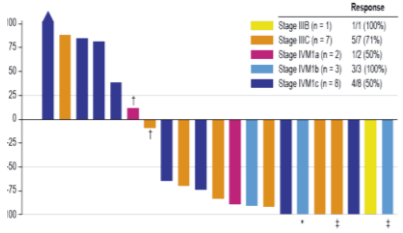
Oncolytic immunotherapy is synergistic with immune checkpoint blockade

- Randomized controlled 198 patient phase 2 study of T-VEC + ipilimumab vs. ipilimumab alone in advanced melanoma
- Response rates more than doubled in combination (38% vs. 18%)
- No additional toxicity as compared to ipilumumab alone Chesney et al JCO, 2017

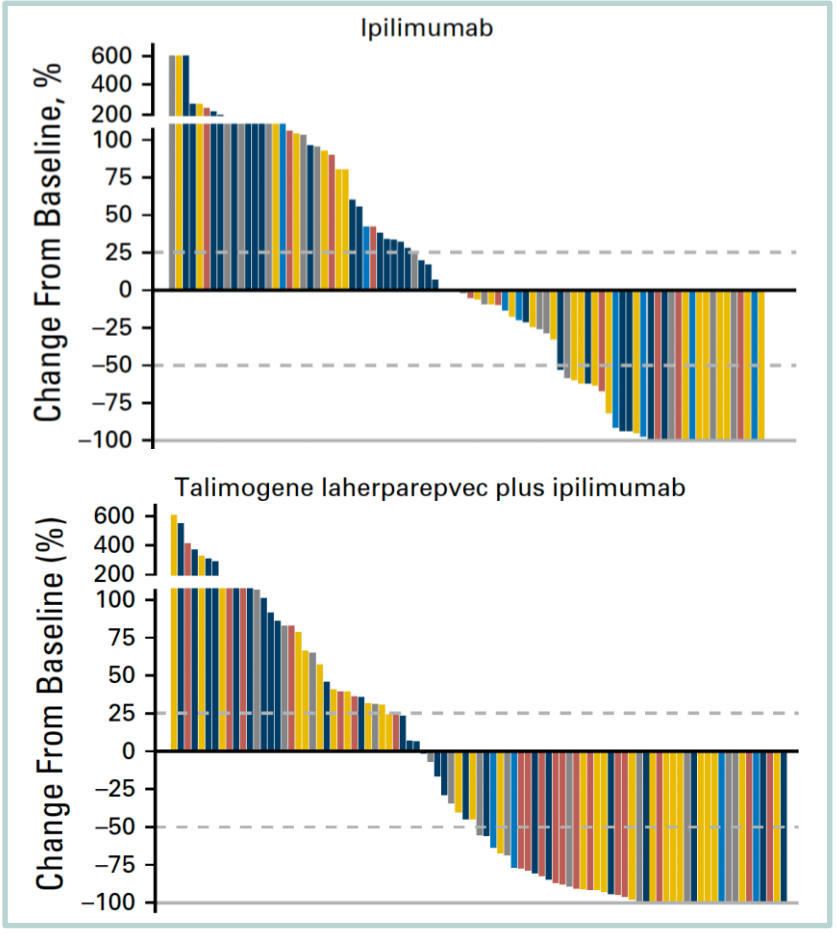
T-VEC+pembrolizumab ph1b study

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

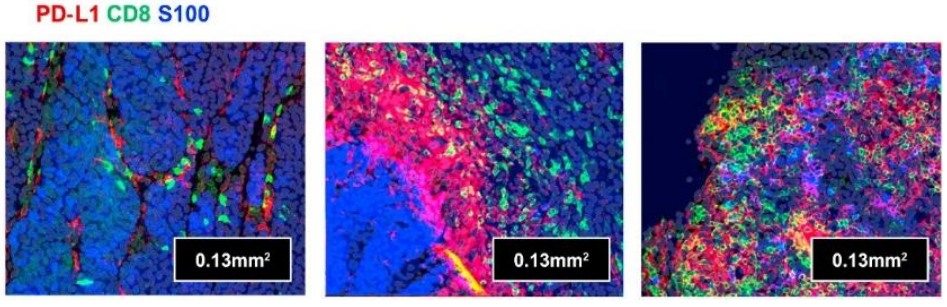


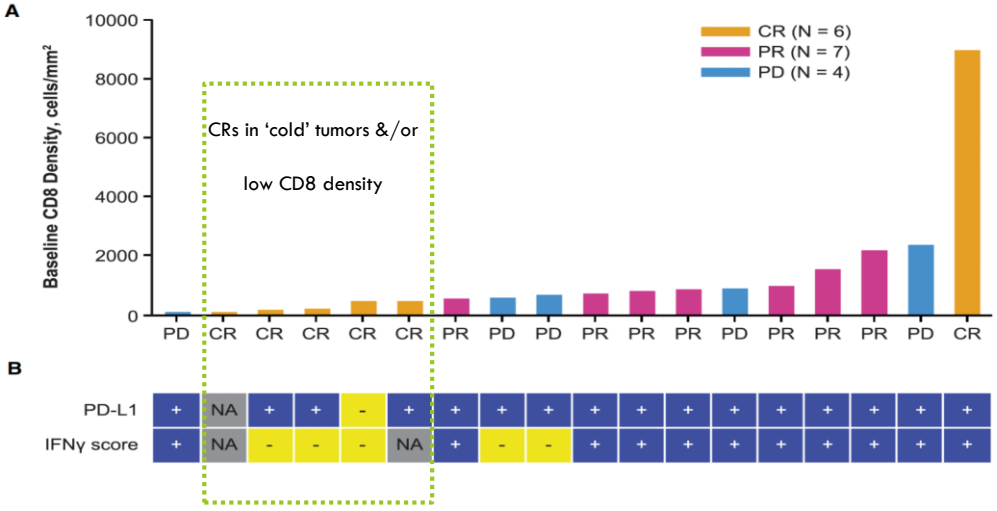
62% response rate; 33% CR rate

Pembrolizumab+T-VEC currently in a >700 patient phase 3 study



Oncolytic immunotherapy turns “cold” tumors “hot”





T-Vec+pembrolizumab

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

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Replimune objectives & vision

- Maximize the effectiveness of oncolytic immunotherapy through
  - Direct tumor killing and intra-tumoral spread
  - Immunogenicity of cell death
  - Anti-tumor immune response generation
  - Loading with multiple immune stimulating genes
    - "Oncolytic immuno-gene therapy"
- Extend the utility of oncolytic immunotherapy beyond melanoma to include most solid tumor types
  - RP1 – 'easier' indications – intended first FDA approval
  - RP2 – 'intermediate' indications
  - RP3 – more challenging indications
  - RP4-n - ?
- Provide the most practical & effective universal combination partners for anti-PD1/L1 drugs providing the *essential* tumor specific immune response without which they can't work

Replimune uses HSV

- HSV has ideal properties for oncolytic immuno-gene therapy:
  - Biology well understood
  - Proven safety & efficacy
    - Includes in combination with immune 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 genome able 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

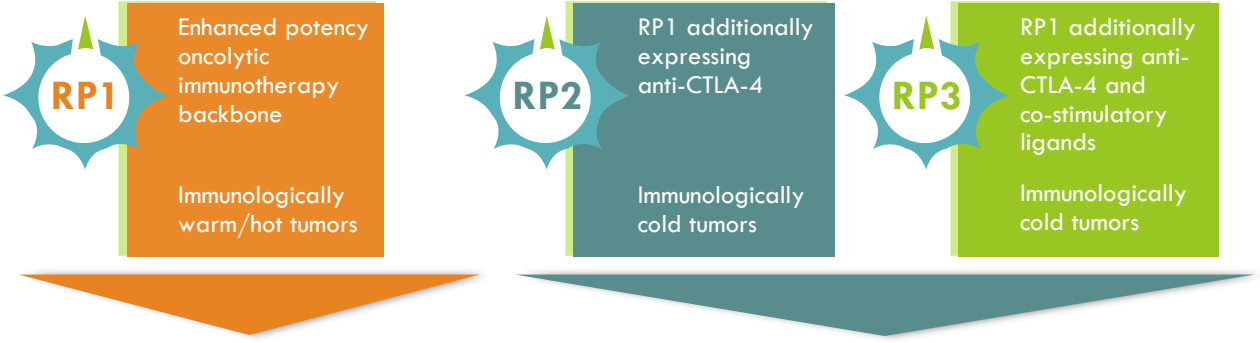
Our Immulytic platform

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

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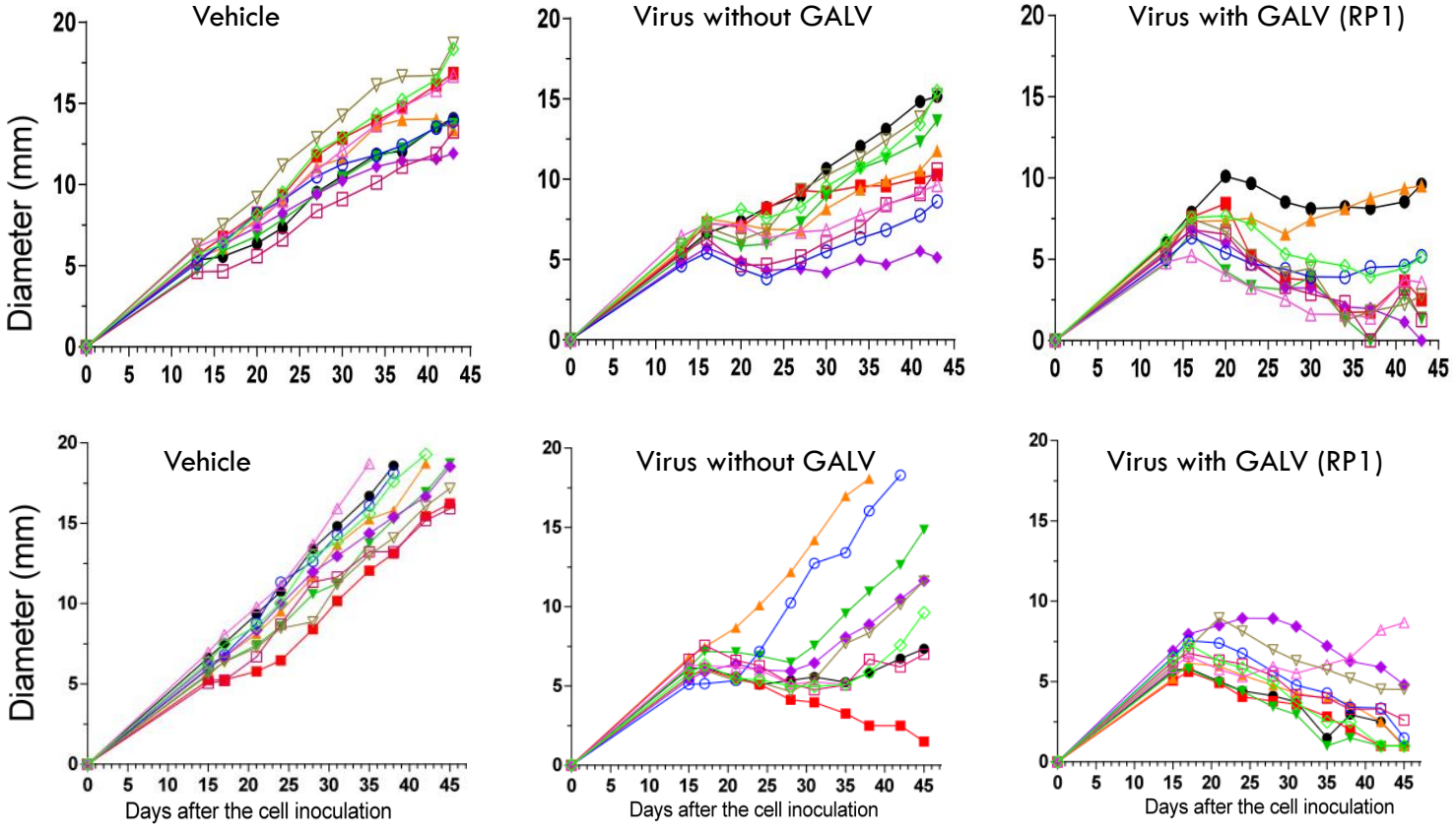
Fusion enhances direct anti-tumor efficacy

A549
lung cancer

MDA-MB-231
breast cancer



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

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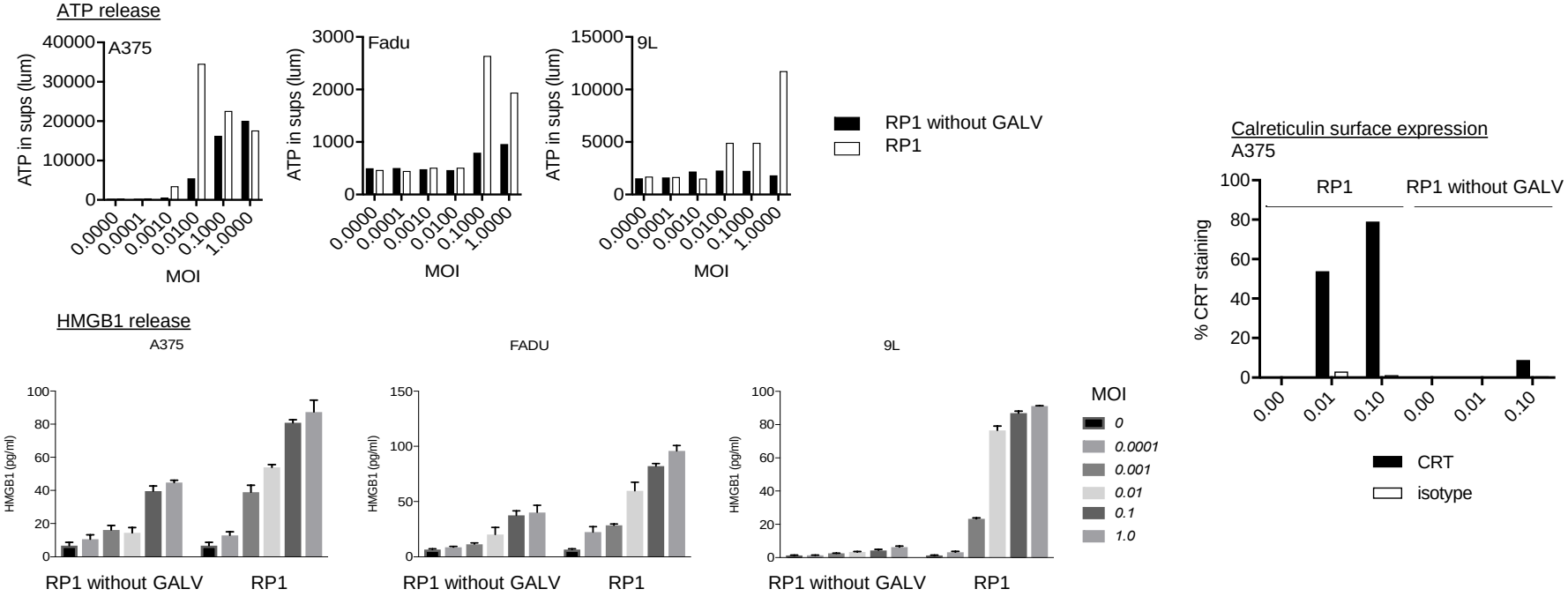
Immunogenic cell death (ICD)

- Immunogenic cell death is necessary for the induction of an effective antitumor immune response as tumor cells die
- Characterized by secretion of damage-associated molecular patterns (DAMPs)
- DAMPs classically used to assess the level of ICD are
  - HMGB1 secretion
    - HMGB1 is a chromatin protein release of which is required for the optimal presentation of tumor antigens to DCs
    - Binds to several pattern recognition receptors on APCs including TLR2 & 4
  - ATP secretion:
    - ATP functions as a "find-me" signal for monocytes
  - Cell surface calreticulin levels
    - Calreticulin is an ER protein only present on the cell surface during ICD

Fusion increases immunogenic cell death



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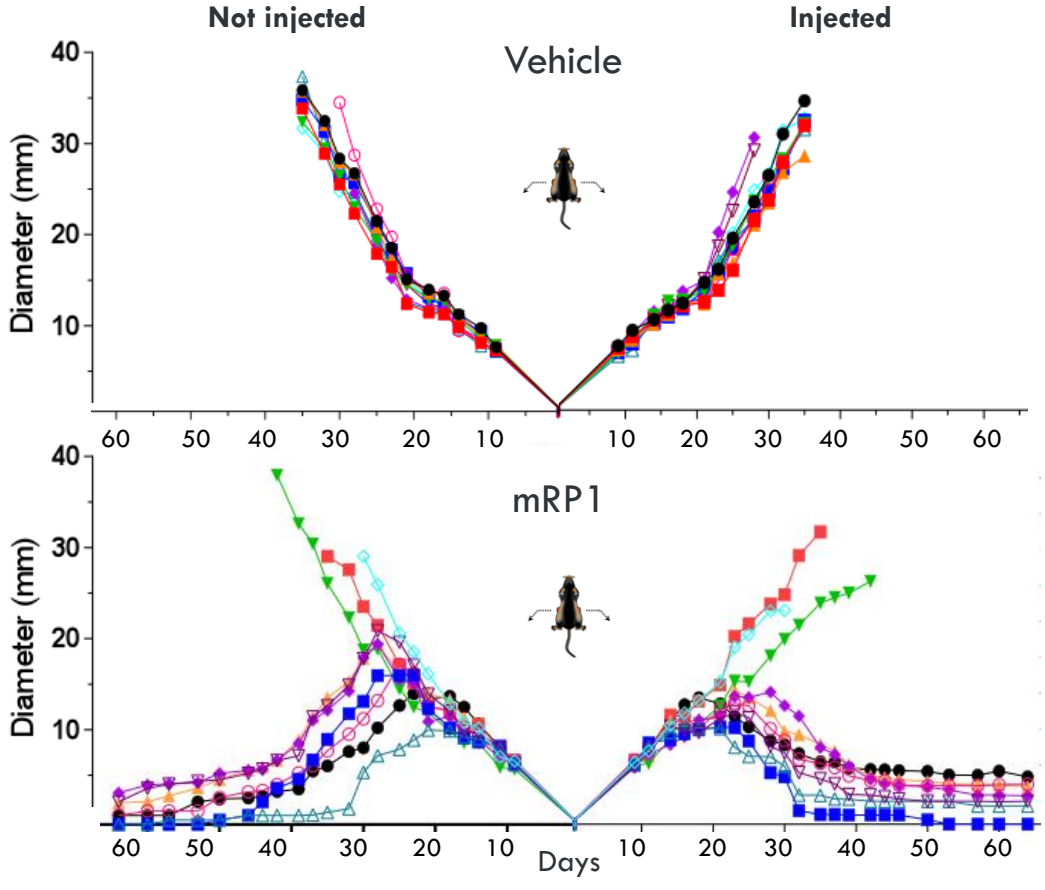
RP1 treats large injected & uninjected tumors



Immune competent rat model (dual flank)

Right flank tumors injected 5x with 5x10^6 pfu

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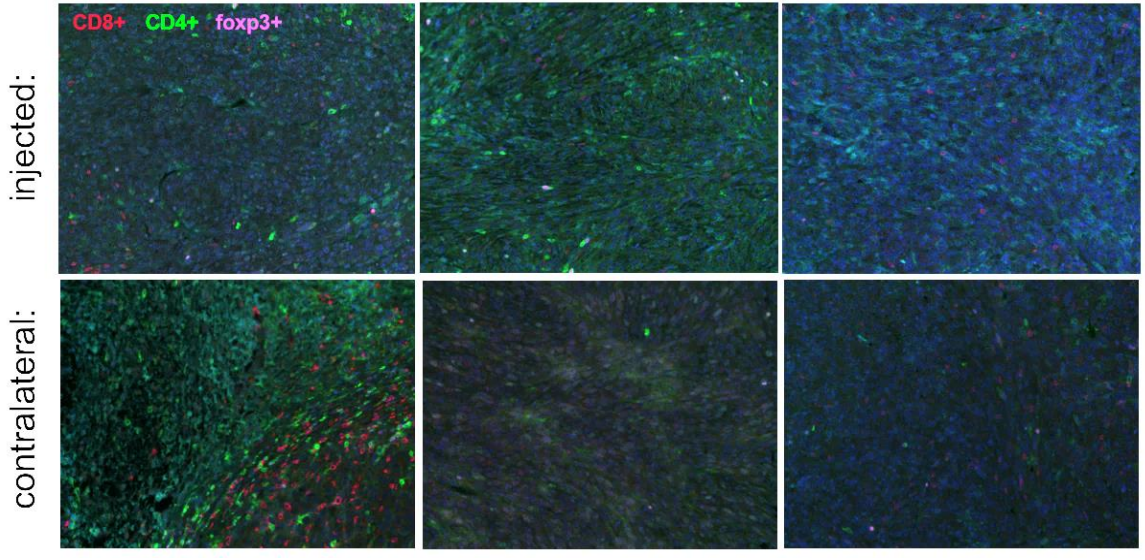
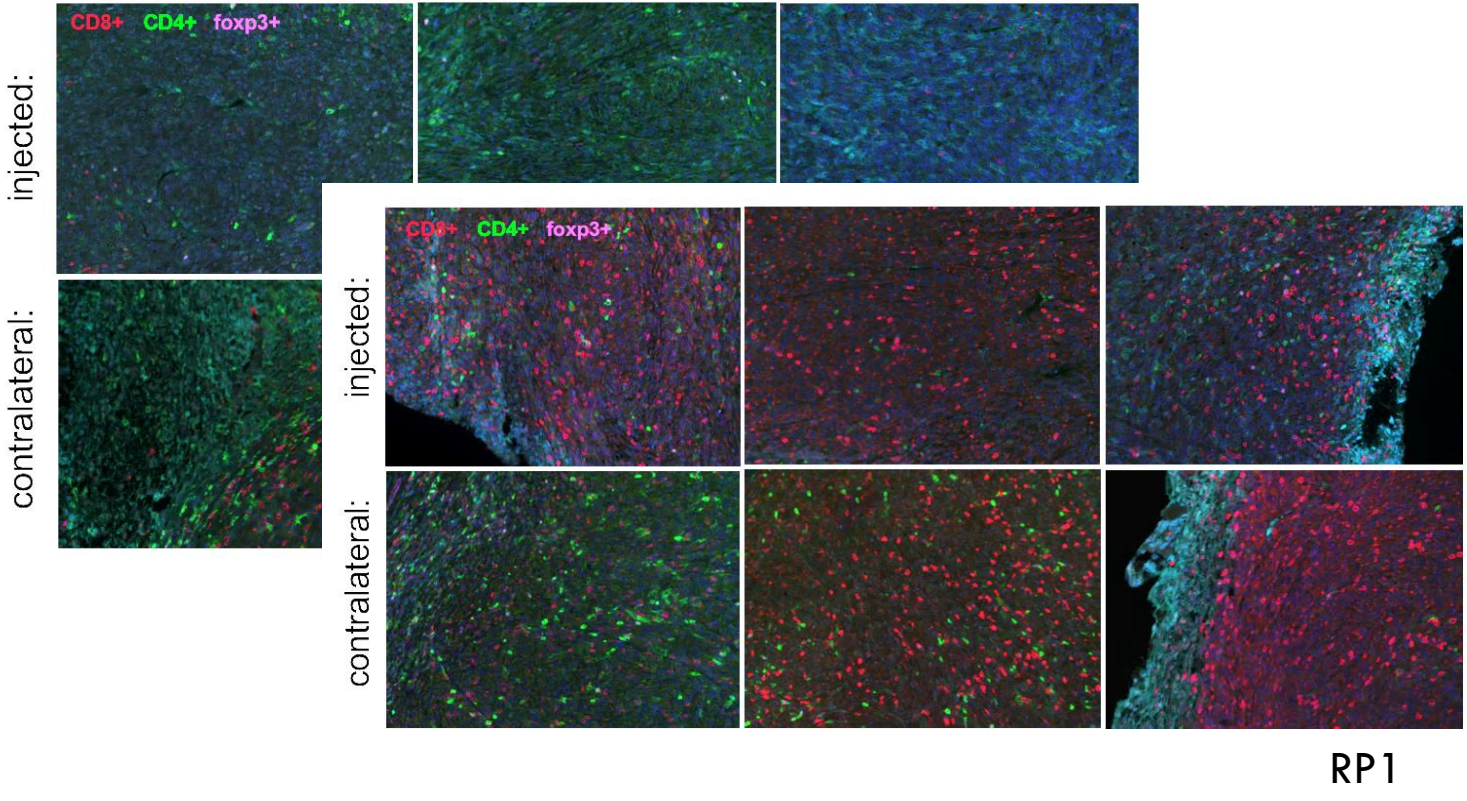
RP1 increases CD8 T cells in injected and uninjected tumors



Vehicle

RP1 increases CD8 T cells in injected and uninjected tumors



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

Potential rapid path to initial approval

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RP1 clinical strategy

Phase 1 (underway)
Safety confirmation & determination of dose for phase 2, all comers
(N≈30)

Phase 2 (initiates H1 2019)
Defined indications
(N≈30 patients per group)

Phase 1/2 clinical trial in ≈150 patients

Single agent RP1

RP1 + nivolumab*[1]

Melanoma + nivolumab*[2]

NMSC[3] + nivolumab*[2]

Bladder cancer + nivolumab*[2]

MSI-H cancers + nivolumab*[2]

EXPAND PROMISING COHORTS (dependent on data & FDA input)

Initiates H1 2019

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

RP1+ cemiplimab vs. cemiplimab alone#

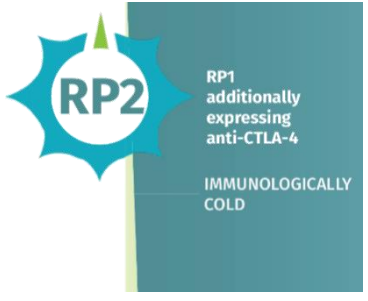
[1] Includes biomarker component to confirm MOA [2] Efficacy to be assessed by ORR, CR rate and biomarker analysis [3] Non-melanoma skin cancers

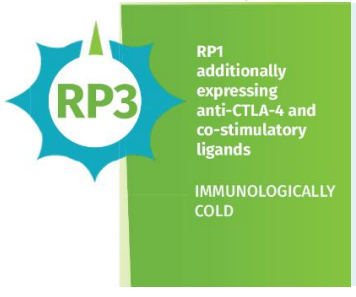
* Under clinical trial collaboration & supply agreement with BMS for the supply of nivolumab

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 – intended initial path to approval

- 4,000-9,000 US deaths annually
  - Expected to overtake melanoma as the most lethal skin cancer
- Anti-PD-1 therapy active
  - Cemiplimab (Regeneron) demonstrated 46% response rate, but low CR rate
  - Recently FDA approved (only approved therapy)
- Tumors are frequently accessible for direct injection
- Highly mutated – contain a lot of neoantigens
- We believe CSCC provides a rapid route to market for RP1
- Preparing for a 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





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

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Intratumoral anti-CTLA-4 & co-stimulatory pathway agonists

- Focus on delivery of proteins which act <u>as the immune response is being generated</u>
  - Systemic antibody approaches probably don't act at the right place or the right time
  - Potential for toxicity
- 

  - Delivery of anti-CTLA-4 directly into the tumor
  - Blocks Treg activation/inhibition of T cell activation at the site of immune response initiation
  - Retain the efficacy of ipilimumab alone & in combination with anti-PD1 but reduce toxicity
    - Potential for improved activity as compared to combination anti-CTLA-4/anti-PD1
- 

  - Delivery immune co-stimulatory pathway activating ligands
  - Antibody approaches have given indications of activity, but toxic
    - Considerable pharma interest in these pathways
  - RP3 encodes GALV-GP-R-, anti-CTLA-4, CD40L & 4-1BBL
    - CD40L: Broadly activates both innate & adaptive immunity
    - 4-1BBL: Promotes the expansion of cellular & memory immune responses

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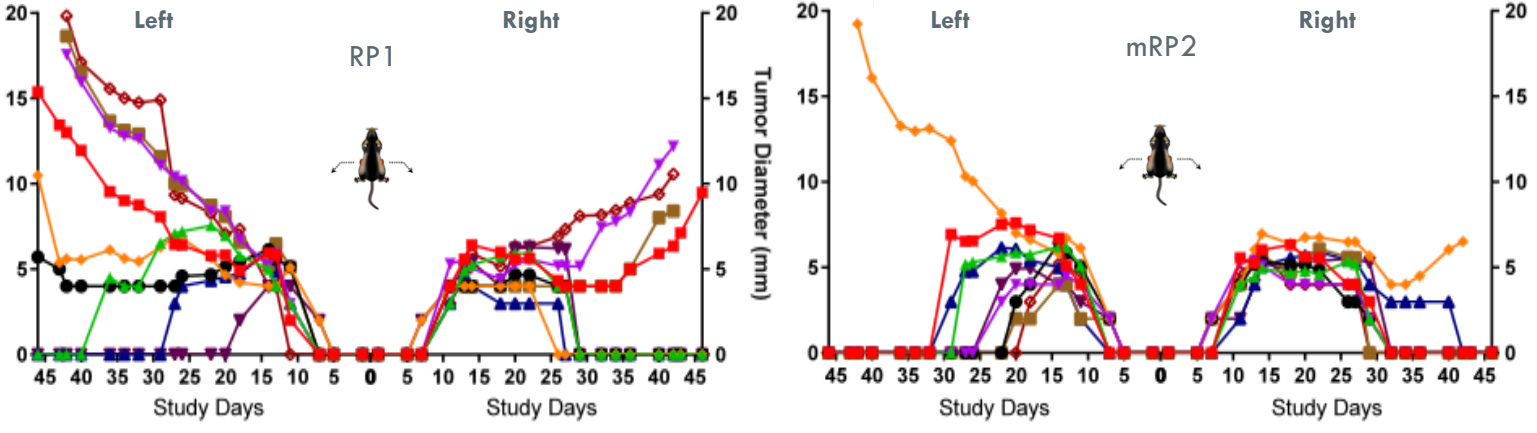
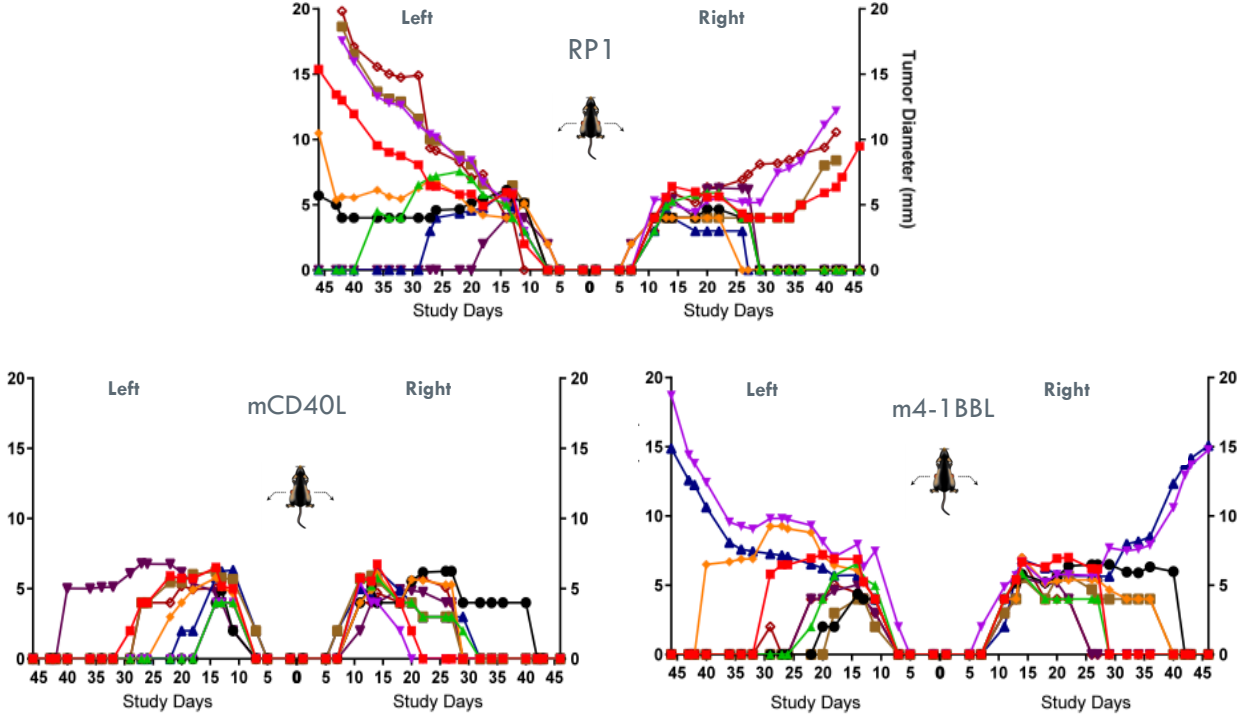
Expression of anti-mCTLA4 enhances efficacy



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

Similarly increased effects with co-stimulatory pathway ligands



Intratumoral anti-CTLA-4 & co-stimulatory pathway agonists

- Focus on delivery of proteins which act <u>as the immune response is being generated</u>
  - Systemic antibody approaches probably don't act at the right place or the right time
  - Potential for toxicity
- RP2 - On track to enter the clinic H1 2019
  - Delivery of anti-CTLA-4 directly into the tumor
  - Blocks Treg activation/inhibition of T cell activation at the site of immune response initiation
  - Retain the efficacy of ipilimumab alone & in combination with anti-PD1 but reduce toxicity
    - Potential for improved activity as compared to combination anti-CTLA-4/anti-PD1
- RP3 - On track to enter the clinic H1 2020
  - Delivery immune co-stimulatory pathway activating ligands
  - Antibody approaches have given indications of activity, but toxic
    - Considerable pharma interest in these pathways
  - RP3 encodes GALV-GP-R-, anti-CTLA-4, CD40L & 4-1BBL
    - CD40L: Broadly activates both innate & adaptive immunity
    - 4-1BBL: Promotes the expansion of cellular & memory immune responses

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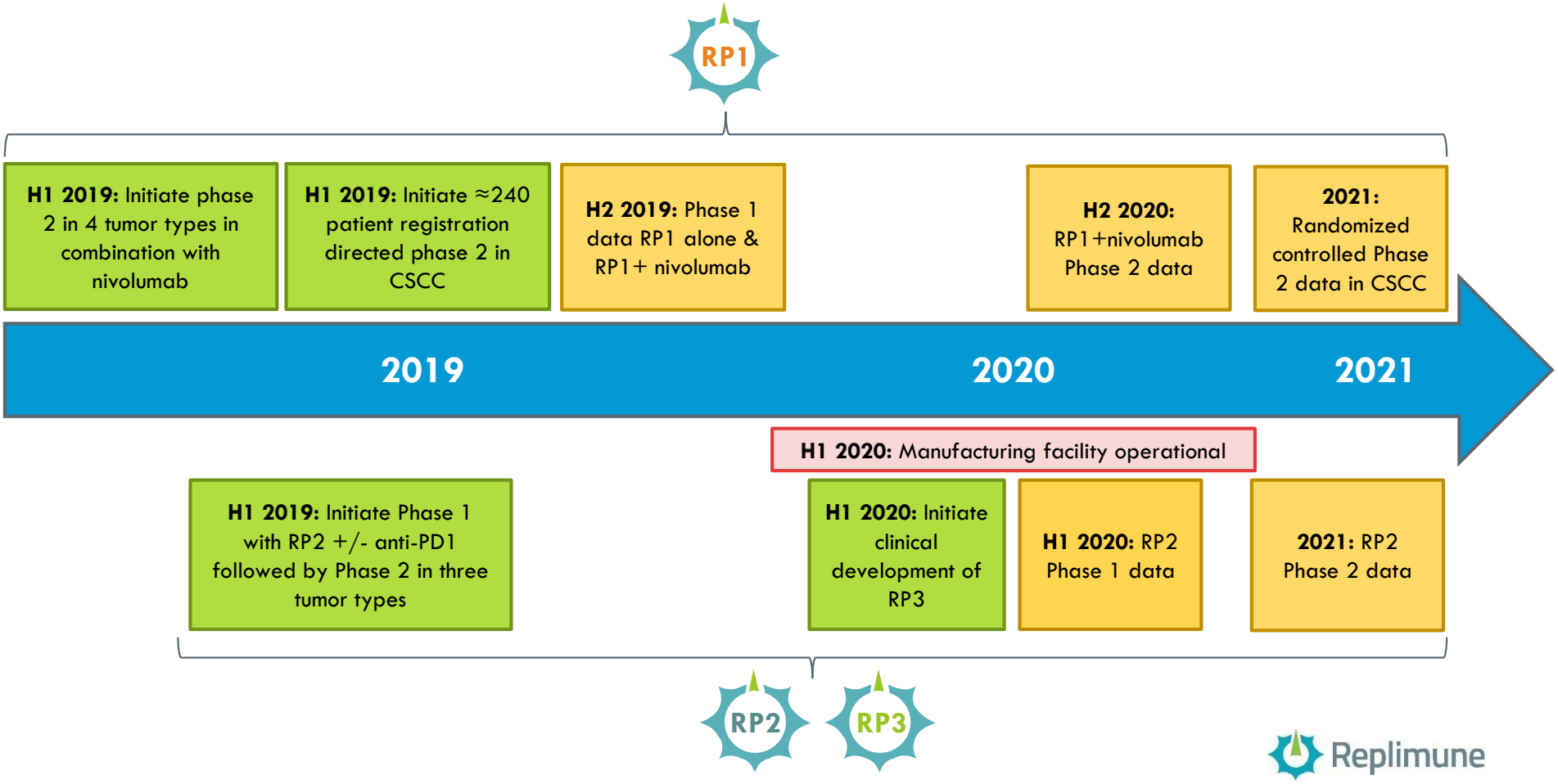
Critical focus on manufacturing

- 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 leased in July 2018 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

* Rendered depiction of the intended final facility

Key target milestones



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Maximally activating the immune system against cancer

- Multi-product candidate oncolytic immunotherapy platform company
- Broad clinical development program underway
- RP1 intended to enter a registration-directed 240 patient phase 2 clinical trial in cutaneous squamous cell carcinoma (CSCC) in H1 2019 (collaboration with Regeneron)
- RP1 being studied in an additional four tumor types in an ongoing 150 patient phase 1/2 clinical trial combining with nivolumab (collaboration with BMS)
- RP2 & RP3 for PD-1/L1 less responsive tumors expected to enter the clinic in 2019/20
- Further product candidates intended
- Commercial scale manufacturing capability being established
- Aim to become a universal combination partner for PD-1/L1 therapies potentially applicable to all solid tumors