SUPERNOVA1 (SNV1), A NOVEL ONCOLYTIC-CELL BASED PLATFORM FOR CANCER THERAPY

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Background

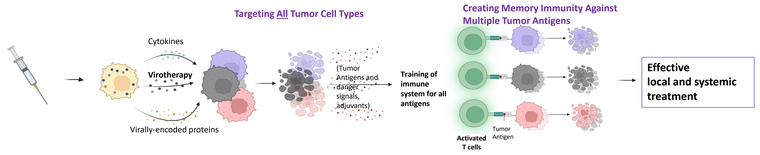
Oncolytic viral immunotherapy utilizes viruses that preferentially infect and replicate within cancer cells, resulting in both tumor cell destruction and activation of an anti-tumor immune response. However, a major obstacle to this approach has been the rapid oncolytic virus (OV) elimination by patient's immune system. Calidi's innovative platform combines allogeneic adipose-derived stem cells (AD-MSC) with an oncolytic virus payload, preventing immune system elimination of the OVs and promoting viral amplification at tumor sites. We demonstrated in a clinical study that patient's own (autologous) stem cells loaded with OVs can be remarkably effective in multiple tumor types, especially in combination with checkpoint inhibitors. However, this approach is very costly and not scalable. Building on this work, we developed an innovative concept called "SuperNova-1, SNV1" (or CLD-201), based on OV-loaded allogeneic stem cells.

Graphic Abstract

Unprotected viruses are quickly eliminated by the immune system before reaching the tumor cells

Calidi's Novel Supernova-1 for efficient delivery and potentiation of oncolytic viruses

Potential of Cell-Based Virotherapy for Universal Impact Across Tumor Types



1 **Supernova is designed to attack tumor using multimodal combination of MOA.**

1- Immunomodulatory (from cells)
2- Oncolytic (Virotherapy)
3- Additional MOA by virally-encoded proteins

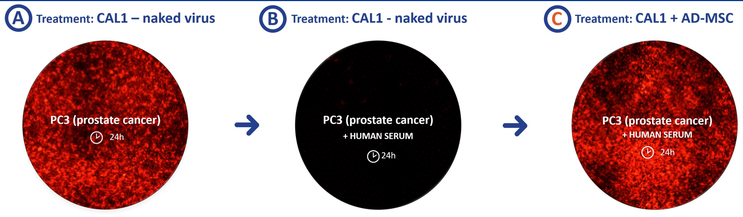
2 **Cell-based virotherapy kills all types of tumor cells (Tumor agnostic).**

1- High therapeutic index of treated lesion/areas (Intratumoral)
2- Low toxicity
3- Strong activation of local and systemic immunity
4- In Situ vaccination

3 **Release of tumor antigens from all tumor types generates a wide and long-lasting anti-tumor immunity.**

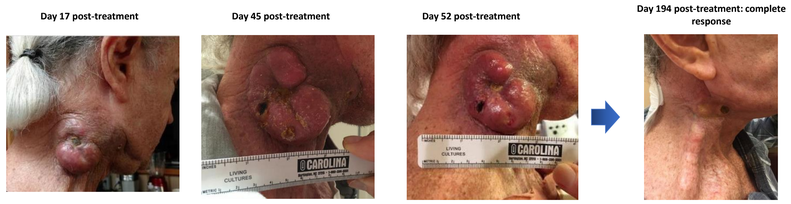
Combination with checkpoint inhibitors will ensure durability of the anti-tumor immune response

SNV Protects Vaccinia Virus Against Human Serum-induced Inactivation



Demonstration of viral-encoding therapeutic proteins expressed in tumor cells when properly protected and delivered by stem cells (Supernova platform). Human prostate cancer cells were infected with CAL1-TurboFP or SNV (AD-MSC+CAL1-turboFP) at MOI of 1. (A) Naked CAL1-TurboFP can efficiently kill tumor cells in media without human serum. (B) However, clinical scenario is dramatically different. Human serum/complement can inhibit the oncolytic virus activity by blocking its capacity to infect and kill tumor cells (20% human serum was added). (C) Treatment efficacy was restored when adipose derived stem cells (AD-MSC) are used to protect and potentiate the oncolytic vaccinia virus.

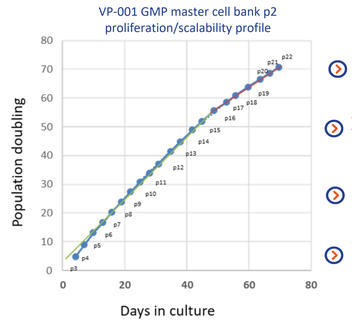
Calidi Autologous Study: Positive Results in Combination With Checkpoint Inhibitor



"Autologous SuperNova," demonstrates robust tumor regression and sustained survival. The subject, a male patient diagnosed with Metastatic Head & Neck Squamous Cell Carcinoma (SCC) at Stage IV_B, exhibited initial resistance to both chemotherapy and radiotherapy. Following the administration of anti-PD-1 treatments, the patient experienced a complete regression of the previously resistant tumor, marking a significant milestone in the intervention. The durable tumor regression persisted, and 194 days after treatment, the patient continued to exhibit full recovery after autologous SNV treatment.

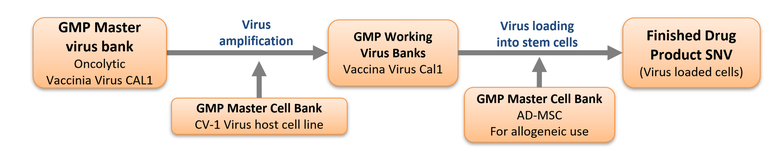
Although successful, autologous approach is costly and not scalable.

Development of Allogeneic Cell-Based Product

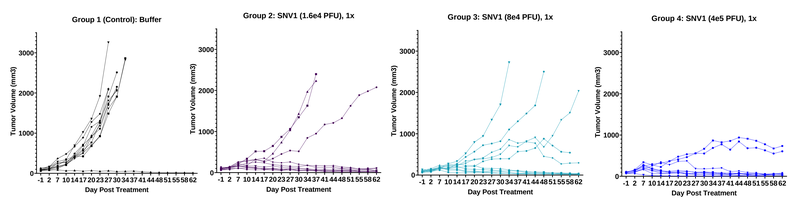


- Calidi owns 8 allogeneic adult adipose (AAA)-derived stem cell (AD-MSC) banks + 1 NSC.
- Allogeneic GMP Master cell bank p2 (VP01), is used in several clinical trials to treat patients with COVID-19-induced acute respiratory distress syndrome (ARDS).
- Optimized manufacturing protocols offer the potential to generate quadrillions of doses of stem cells from a single donor.
- Single donor can be used for multiple indications, clinical development programs and commercialization (Scaled-up VP-001 cells maintained: genetic stability, biological activities.

Unveiling the Manufacturing Process of Allogenic SNV1

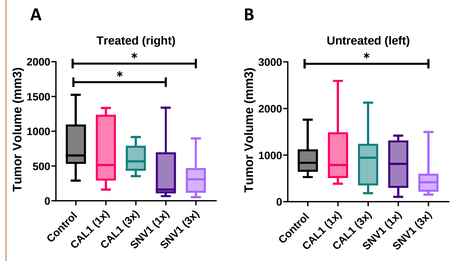


Therapeutic Efficacy of SNV1 at different dose concentrations



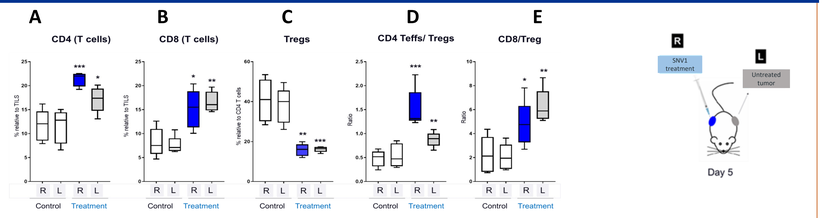
Inhibition of Tumor Growth by SNV1 Treatment in Triple Negative Breast Cancer (MDA-MB-231) Xenograft Model. Athymic nude mice were subcutaneously inoculated with MDA-MB-231 cells in the right flank. Once tumors reached 60-100 mm3, animals were intratumorally treated with a single dose of SNV1 at varying concentrations (1.6e4 PFU, 8e4 PFU, 4e5 PFU) or buffer control (n=10 per group). Individual tumor growth data is presented, revealing significant tumor shrinkage in all SNV1-treated groups compared to the control. Notably, even a single injection of a very low SNV1 dose (1.5e3 cells, approximately 10 PFU per cell) resulted in substantial tumor inhibition. The findings demonstrate a dose-dependent effect, indicating the potential of SNV1 in inducing significant inhibition of tumor growth.

Intratumoral administration of SNV1 induces strong and durable systemic antitumor immunity



SNV1 inhibits treated and distant untreated tumors. Female BALB/c mice were inoculated murine colon cancer cells (CT26) in the right and left abdominal flank regions. Once tumors reached the volume about 50 mm³, animals were treated with $1x10^6$ SNV1 cells (10 PFU/cells) or with $1x10^7$ PFU of CAL1 vaccinia virus one or three times, every 2 days. Only right tumor was treated. Box plot data shows both right and left tumor size 12 days after treatment. Statistical significance was analyzed between treated groups compared to control group using nonparametric Mann-Whitney test, *P < 0.05

SNV1 Modulates Local And Distant Tumor Immune Infiltration



Tumor infiltrating lymphocyte (TIL) analysis in treated and untreated tumors. Five days after the treatment, tumors from 5 controlled and 5 treated animals were excised and enzymatically digested to isolate TILs. The flow cytometry analysis demonstrated statistically significant treatment-related proportional increases in the fractions of total infiltrating CD4 (**A**) and CD8 (**B**) T cells and decreases in the CD4+CD25+Foxp3+ Tregs (**C**). The changes in the T cell compartment were further associated with improved ratios of CD25+Foxp3- CD4+ Teff to Tregs (**D**) and CD8 T cells to Tregs (**E**). These changes in the TME are consistent with conditions favoring direct and indirect oncolysis through potentiation of adaptive anti-tumor immunity. Moreover, similar favorable changes in the fractions or ratios of immune infiltrates can be observed in both the treated (right) and distant untreated tumors (left), providing mechanistic basis for the observed potent abscopal effects.

Graphic clinical trial design for Allogenic SNV1 (CLD-201)

Phase 1 – Dose finding (3+3), Safety & Shedding.

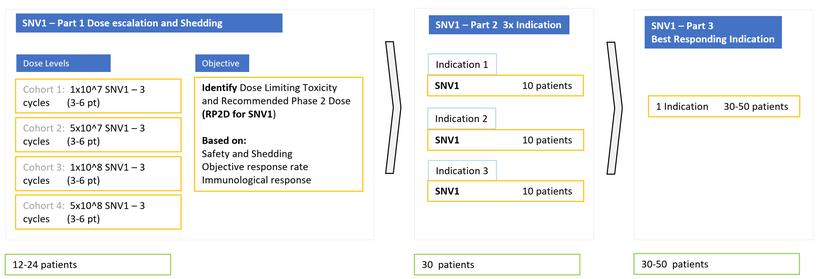
- Indications: Advanced Metastatic Solid Tumors – all comers
- Treatment: Intratumoral injections of SNV1 on Week1/Day 1, Week 3/Day 1, and Week 5/Day 1

Phase 1b – Dose Expansion

- Objective: To determine the best responding indication for Part 3 in 3 selected indications (10 patients)
- Dose: Dose identified in Part 1
- Treatment: Same as Part 1

Phase 2 - Best Responding Indication

- Objective: Evaluate ORR in 1 indication (30-50 patients)
- Dose: Dose identified in Part 1
- Treatment: Same as Part 1



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