Haptenized Vaccines for Viral Diseases and Cancer

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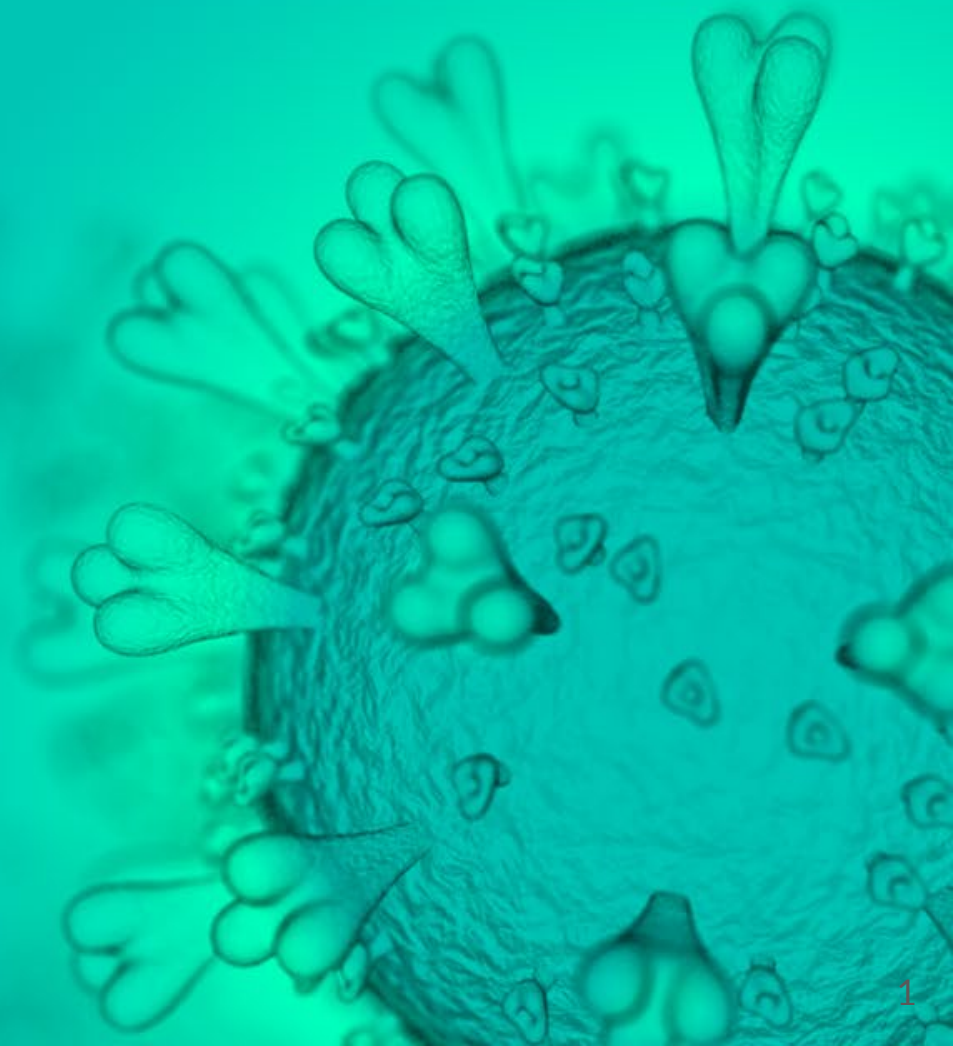
World Vaccine & Immunotherapy Congress



Haptens

- Simple chemicals that are incapable of inducing immune responses by themselves but become immunogenic when attached to a protein carrier
- Discovered by Karl Landsteiner: Immunization with a hapten modified protein induces an immune response against the hapten-protein conjugate
- Weigle: Immunization with a hapten-modified protein breaks artificial and natural tolerance to that protein
- Examples of haptens:
    - Dinitrophenyl (DNP) – binds to hydrophilic amino acids
    - Sulfanilic Acid (SA) – binds to hydrophobic amino acids

DNP-Modified Covid-19 Vaccine: BVX-0320

Murine Proof of Concept Model

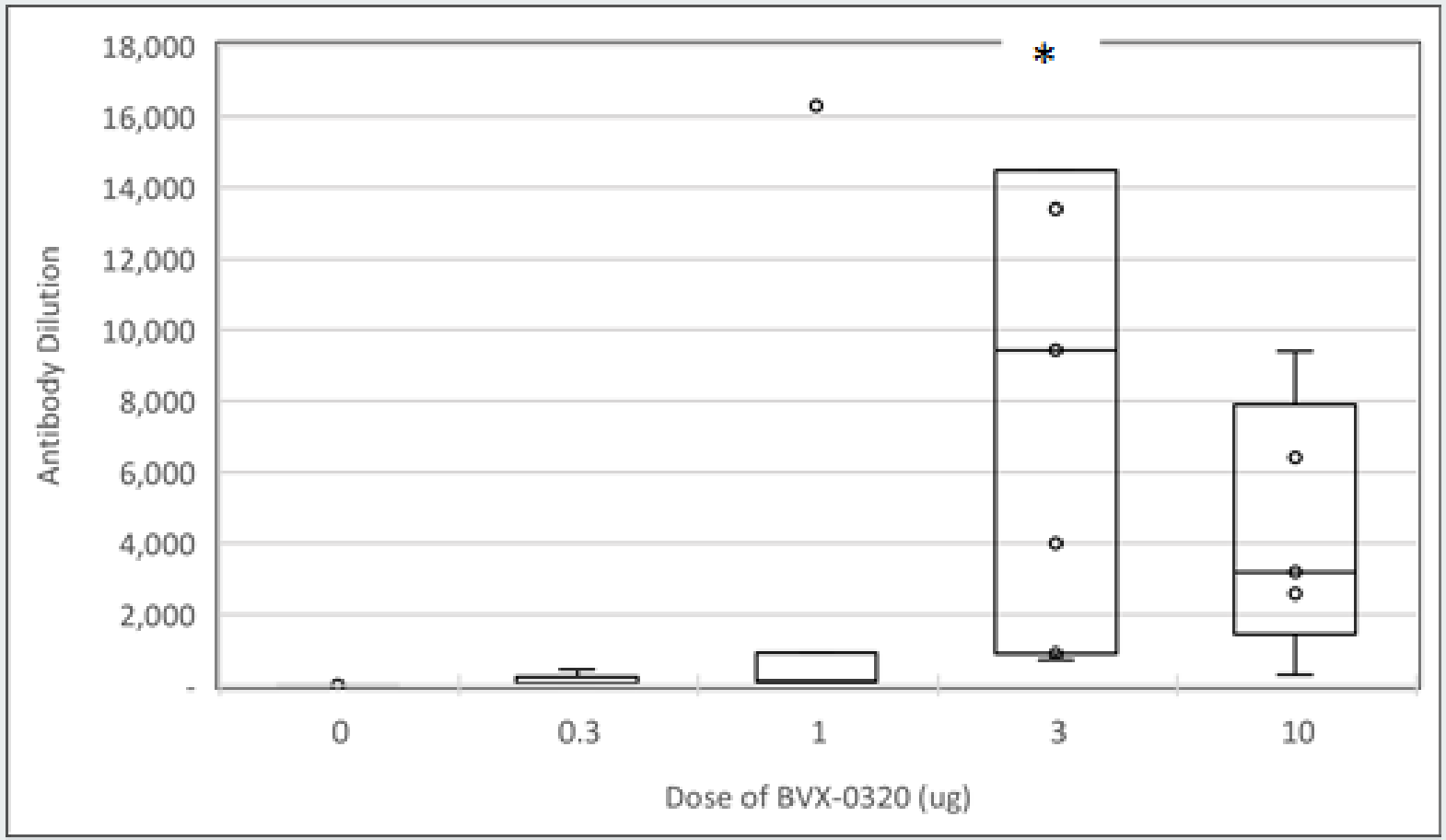
- The S1 subunit of the spike protein of SARS-Cov-2 was modified with DNP by reacting with dinitrobenzene sulfonic acid.
- BVX-0320 was mixed with the adjuvant QS21 10ug before sc injection.
- Male CF-1 mice (7 per group) were assigned to receive adjuvant alone or BVX-0320 + adjuvant at one of four doses: 0.3ug, 1.ug, 3.ug, or 10ug.
- Doses were administered on days 1 and 28.
- Serum was collected on days 1 and 42; the mice were sacrificed, and spleens harvested on day 42

Haptenized Covid-19 Vaccine - Results

Two injections of BVX-0320 + adjuvant induced:

- Antibody that bound to unmodified S1 subunit by ELISA
- T cell response as indicated by λ interferon production after secondary stimulation with S1 peptides
- T cell response as indicated by induction of activation markers, CD25 and CD69, on both CD4+ and CD8+ T cells
- A dose-response relationship with highest responses after BVX-0320 doses of 3ug or 10ug and lower or no responses after 1ug or 0.3 ug
- No observable toxicity

Haptenized Covid-19 Vaccine – Antibody Response



*Titer 1:120,00

0.3ug group vs. 3ug group, p=.002

1ug group vs. 3ug group, p=.041

3ug group vs. 10ug group, p=.522

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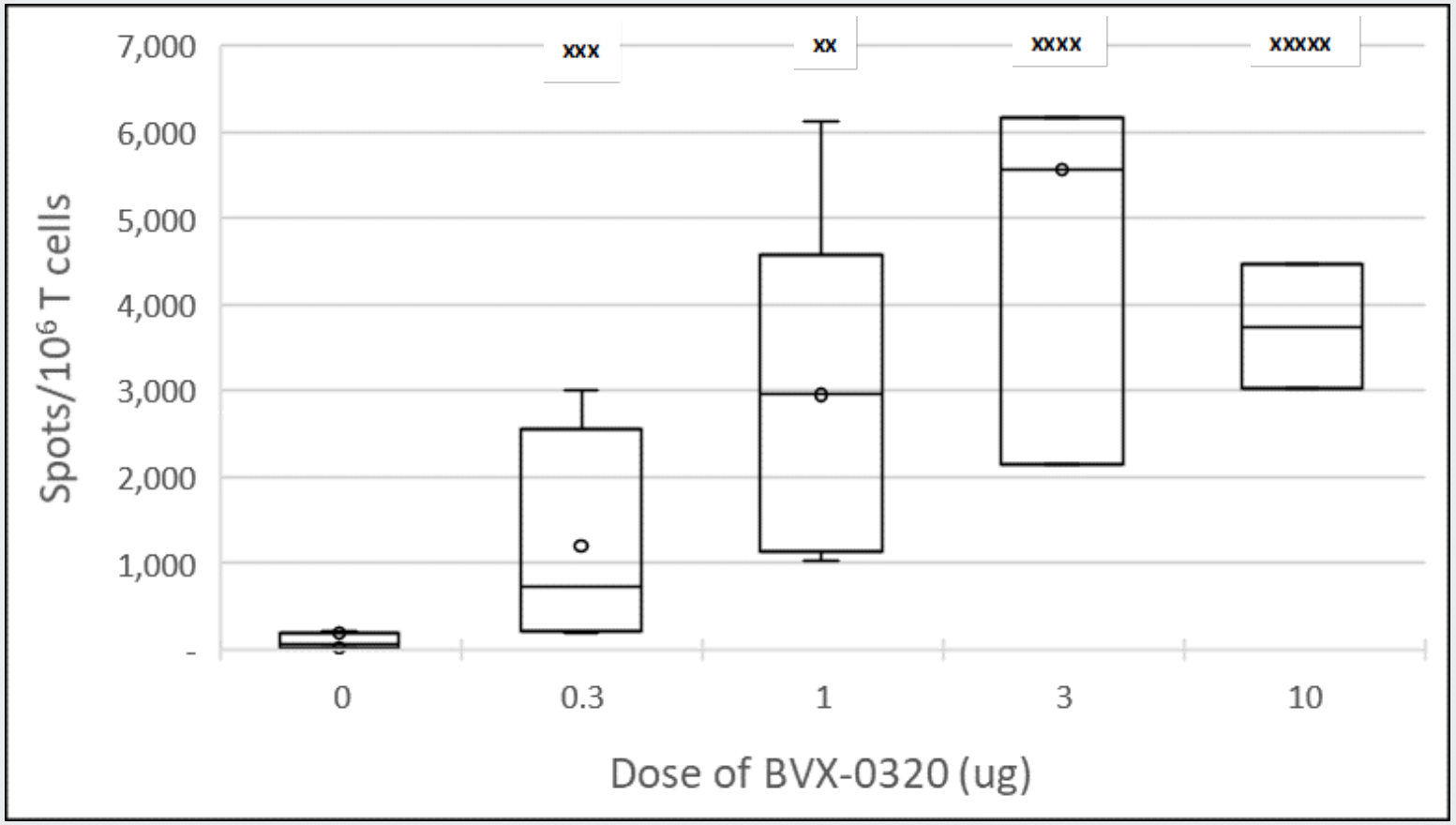
Haptenized Covid-19 Vaccine – T Cell Response
ELISPOT: gamma interferon



x: spleen cells with > 7,000 spots/million

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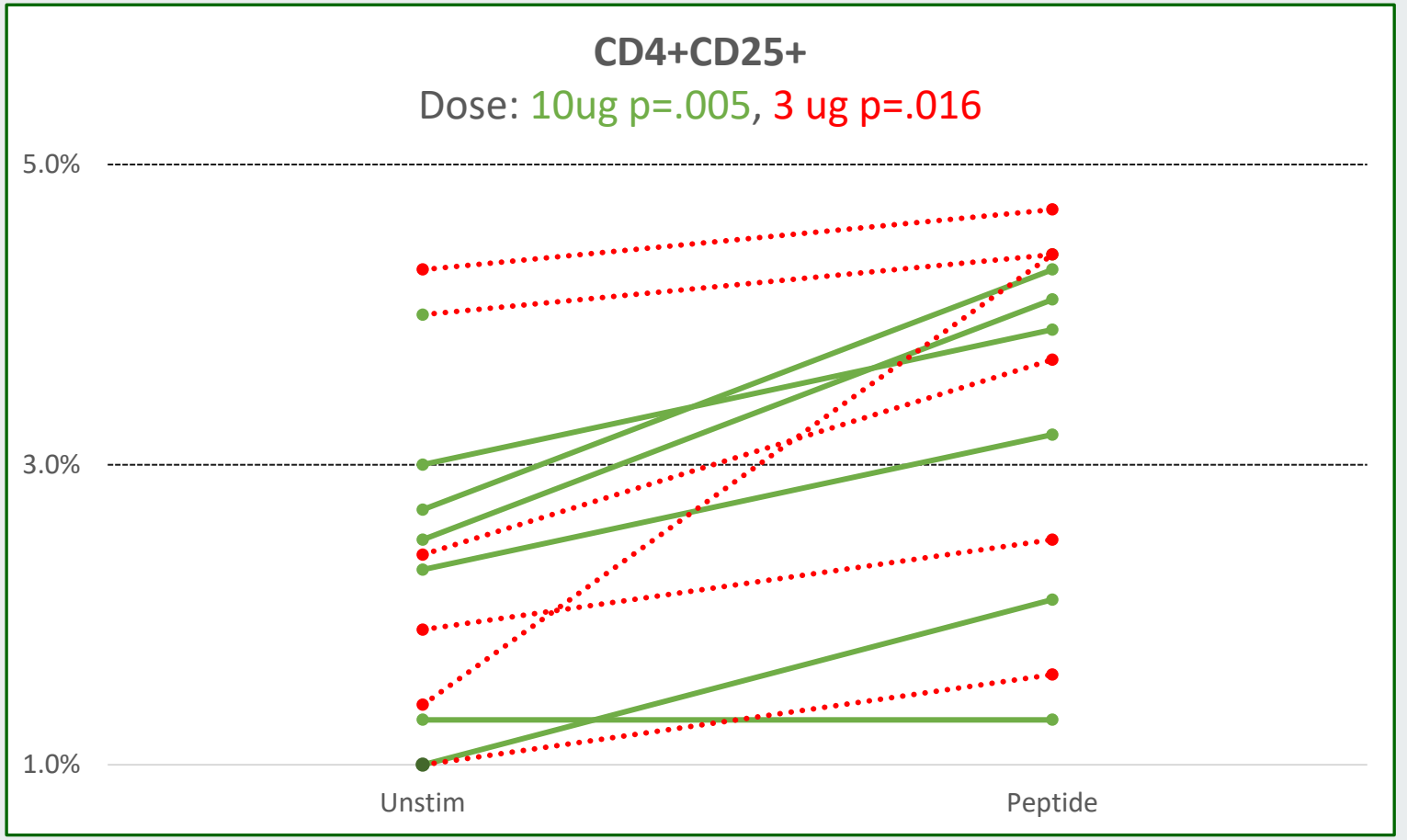
Haptenized Covid-19 Vaccine – T Cell Response

Activation – CD4+CD25+



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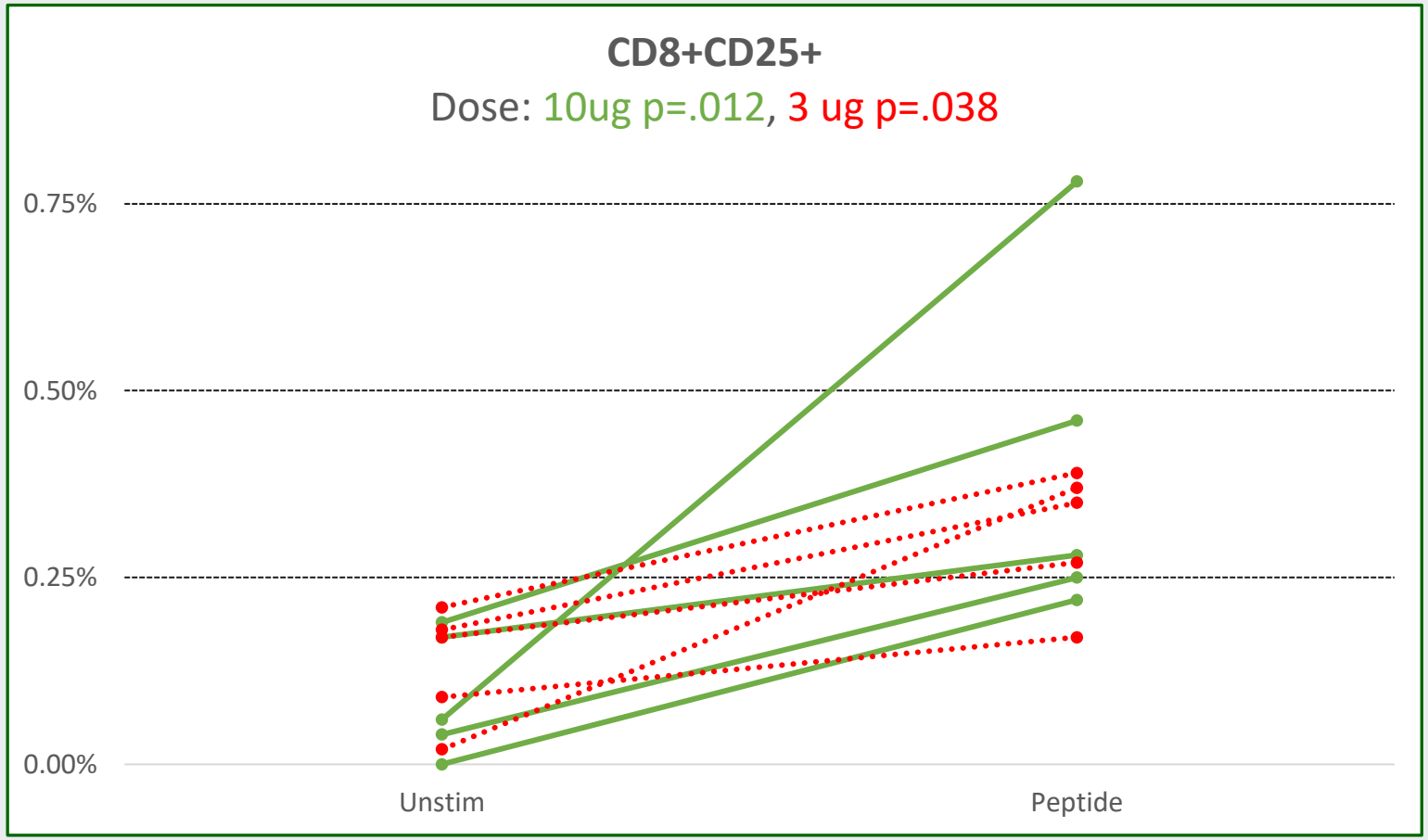
Haptenized Covid-19 Vaccine – T Cell Response

Activation – CD4+CD25+



Clinical Trials of First Generation Haptenized Cancer Vaccines Not Performed by Biovaxys

Melanoma:	
DNP-modified, Stage IV:	97*
DNP-modified, Stage III adjuvant:	214
DNP-modified, Other studies:	96
Bihaptenized, Stage IV	23*
Total Melanoma	430
Ovarian Cancer:	
DNP-modified, Stages III and IV – phase I	30
DNP-modified, Stages III and IV – phase I-II	26*
Total Ovarian Cancer	56

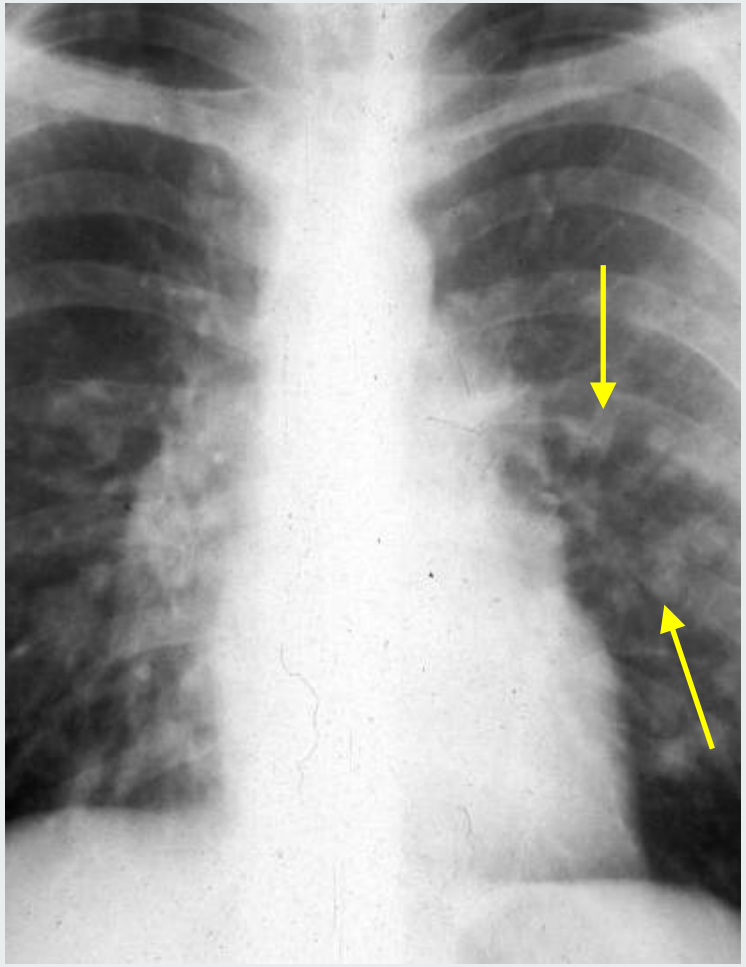
*Study results shown on following slides.

Results of a Trial of DNP-Modified Vaccine in Patients with Stage IV Melanoma

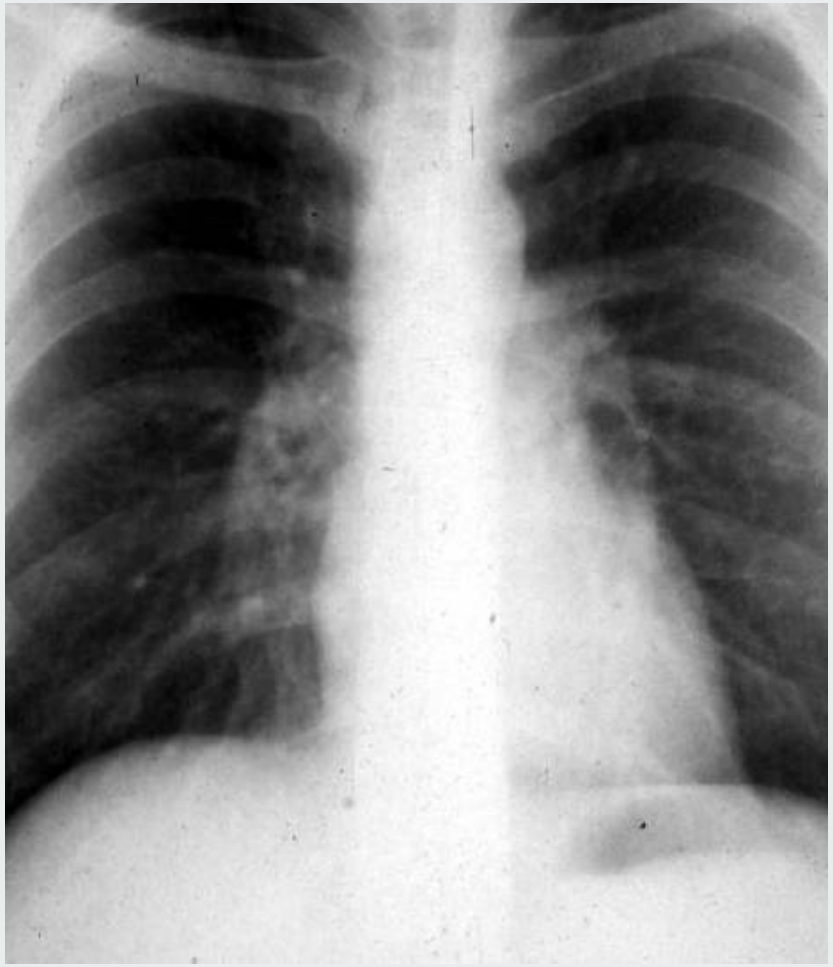
- 83 patients with stage IV, surgically-incurable melanoma
- Received multiple injection of autologous, DNP-vaccine with BCG adjuvant
- Tumor regression assessed by standard criteria
- 11 anti-tumor responses – 2 CR, 4 PR, 5 Mixed
- Responses most common in lung metastases
- Response durations: CR – 12 and 29 months; PR – 5,6,8,47+ months
- Responses associated with longer survival than non-responders.
- No safety issues
- Publication: Int. J. Cancer, 94:531, 2001

Complete Regression of Melanoma Lung Metastases After DNP-Modified Vaccine

Pre-Vaccine



4 Months Post-Vaccine



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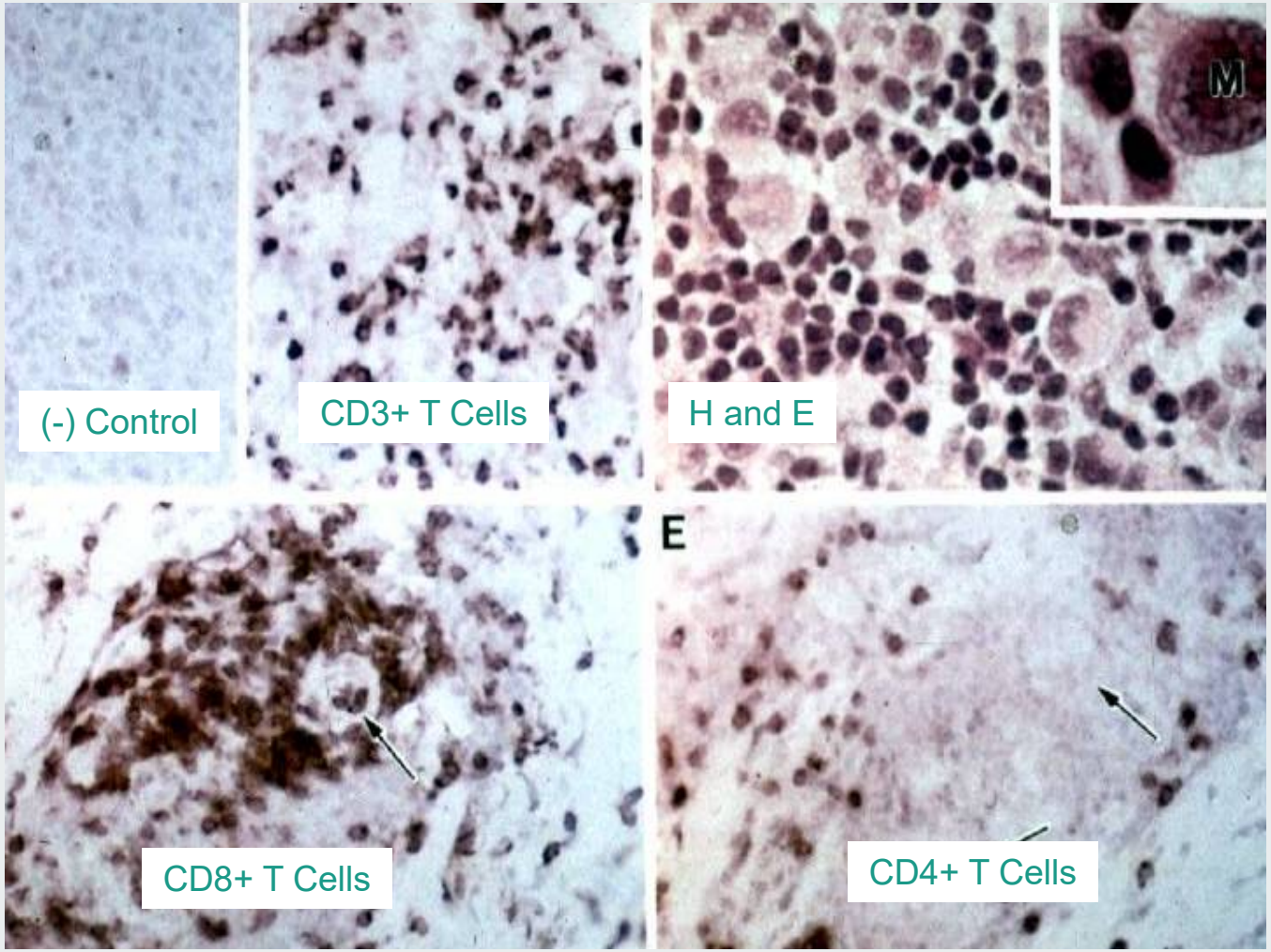
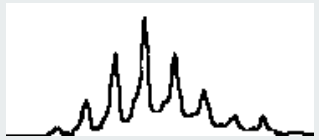
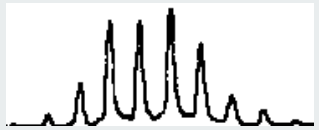
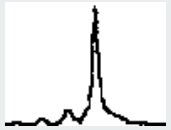
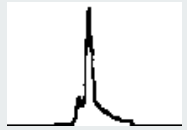
T Lymphocyte Infiltration of Metastatic Tumors After DNP-Modified Vaccine



Clonality of T Cells Infiltrating Melanoma Metastases

	Vß4-Cß	Vß4-Jß2.1	
PBL			polyclonal
Tumor			monoclonal

CDR3 size distribution patterns of Vß-4 structures analyzed with fluorescent Cß and Jß 2.1 primers in T cells infiltrating metastasis and matched PBL

Publication: J. Immunol., 169:3407-3412, 2002.

Results of a Phase I-II Trial of DNP-Modified Vaccine in Patients with Advanced Ovarian Cancer

Efficacy:

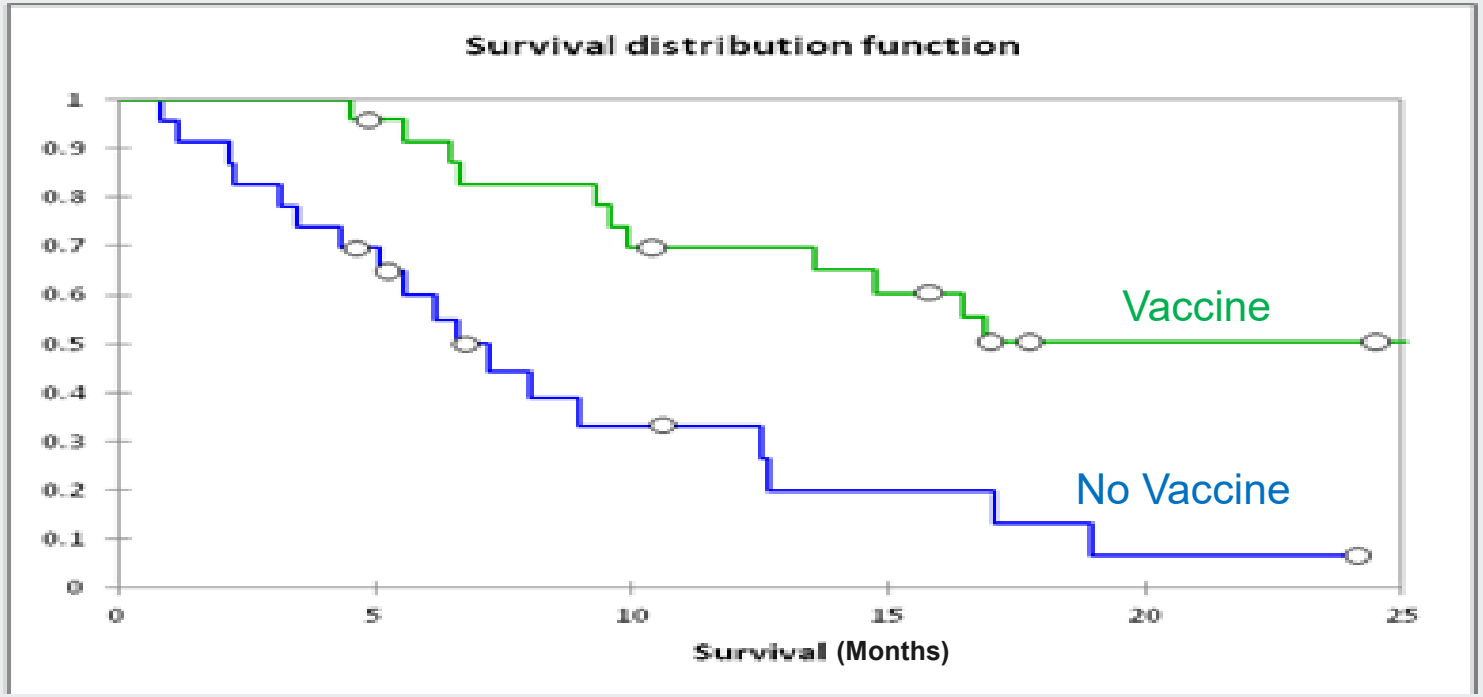
- 26 evaluable patients with advanced, chemotherapy-resistant ovarian cancer
- Received multiple injection of autologous, DNP-vaccine with BCG adjuvant
- Median survival: 25.4 months with >20% 5-year survivors

Safety:

- No Serious Adverse Events attributed to vaccine
- Most commonly Adverse Events: injection site reactions, mainly grade I and II
- No evidence of auto-immunity
- No safety issues of concern to FDA

Publication: Gynecologic Oncology, 134:428, Abstract 25, 2014

Results of a Phase I-II Trial of DNP-Modified Vaccine in Patients with Advanced Ovarian Cancer



Overall survival of patients who received vaccine (25.4 months) vs patients who had vaccine prepared but did not receive vaccine (6.5 months); p=0.001

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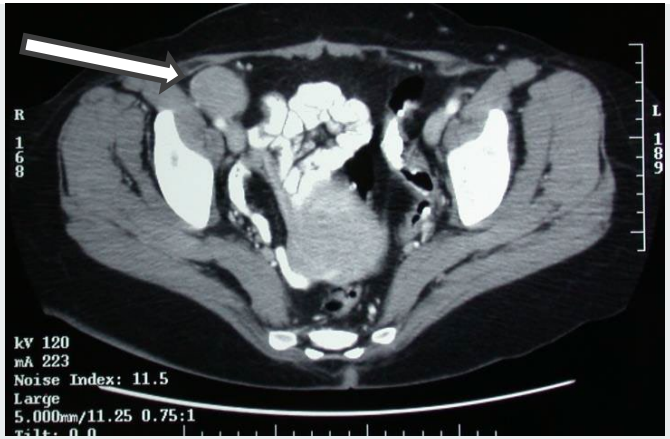
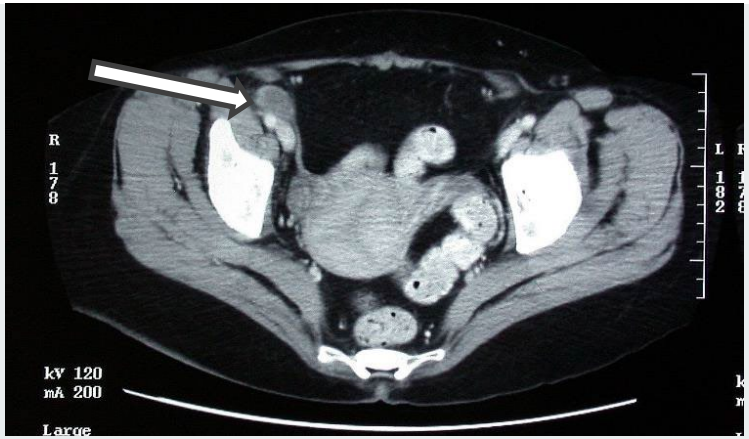
Results of a Phase I Trial of *Bihaptenized* Vaccine in Patients with Stage IV Melanoma

- Autologous melanoma cells were extracted from excised metastatic tumors.
- Half the cells modified with dinitrophenyl (DNP) and half with sulfanilic acid (SA).
- DNP- and SA-modified cells were combined, fixed in 37.5% ethanol, and frozen.
- Patients had stage IV, surgically incurable, melanoma.
- Excellent safety profile: No serious adverse events were observed.
- At the highest dose of vaccine tested, 8/10 patients developed T cell response (delayed-type hypersensitivity-DTH) to both DNP-modified and SA-modified autologous melanoma cells, while 6/10 developed DTH to unmodified autologous melanoma cells.
- Of 15 patients with measurable metastases, antitumor responses were: PR=1, MR=2, Stable=1

Pre-Vaccine



Post-Vaccine - PR



Conclusions

- Covid-19 vaccine comprised of recombinant S1 subunit of the spike protein modified with DNP induced antibody and T cell responses to the unmodified protein.
- Melanoma vaccine comprised of autologous tumor cells modified with DNP induced regression of metastases, associated with clonal T cell infiltration of metastatic sites.
- Ovarian cancer vaccine comprised of autologous tumor cells modified with DNP appeared to prolong survival in patients with chemotherapy-resistant disease.
- Bihaptenized (DNP + SA) autologous vaccine was shown to be feasible and immunogenic in patients with metastatic melanoma.
- No safety issues have been observed in any haptenized vaccine trials.

Planned Phase I Study of Autologous Bihaptenized (DNP + SA) Vaccine (BVX-0918) in Advanced Ovarian Cancer

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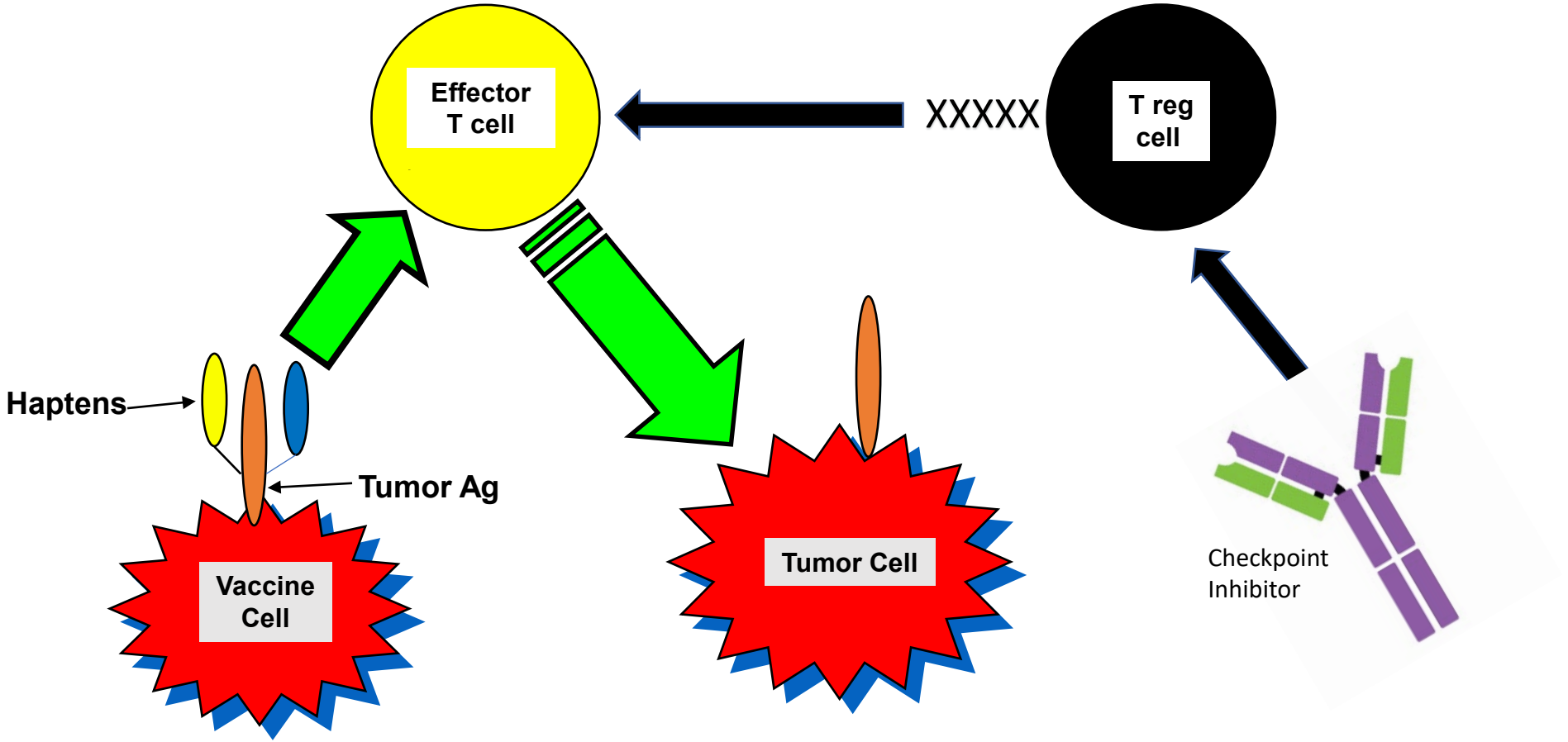
- 30 patients with advanced, chemotherapy-resistant ovarian cancer
- Tumor tissue obtained and vaccines manufactured in GMP lab in France
- Vaccine cells modified with two haptens:
  DNP – modifies hydrophilic amino acids
  SA – modifies hydrophobic amino acids
- Primary endpoint is safety, but survival and CA-125 levels will be measured
- Study to be performed in Europe
- Clinical partner and sponsor
  Procare Pharmaceuticals, Barcelona
- Study to begin Q3 2022

Future Directions - I

- Combine BVX-0918 with a checkpoint inhibitor



Future Directions - II

- Apply bihaptenized tumor cell vaccine technology to other human cancers, e.g., colorectal cancer
- Study the specificity of T cells obtained from vaccinated cancer patients to identify new cancer antigens
- Apply DNP-modified viral protein technology to other viruses, e.g., HPV and influenza
- Develop a pan-sarbecovirus vaccine by serial immunization with DNP-modified spike protein components from SARS-Cov-1 and SARS-Cov-2