

# The Application Protocol of CpG ODNs

- Edited by **InvivoGen**

## Three Classes of CpG ODNs

CpG ODNs are short synthetic single-stranded DNA molecules with unmethylated CpG oligodeoxynucleotides (ODNs) in particular sequence contexts (CpG motifs). They are recognized by the Toll-like receptor 9 (TLR9) and have been extensively studied as vaccine adjuvants.

Three classes of CpG ODNs: Class A (Type D), Class B (Type K) and Class C.

Class	Structure	Applications
<b>Class A</b>	One PO central CpG-containing palindromic motif and one PS-modified 3' poly-G string	- Stimulation of pDCs - Induction of IFN- $\alpha$ production
<b>Class B</b>	a full PS backbone with one or more CpG dinucleotides	- Stimulation and proliferation of B cells - NF- $\kappa$ B activation in TLR9-expressing recombinant cells - <b>Vaccine adjuvant</b>
<b>Class C</b>	a complete PS backbone and a CpG-containing palindromic motif, combining the features of Class A and B CpG ODNs	- Combined applications of A-class and B-class CpG ODNs

## Protocol in Mice Tumor Models

PRODUCT	MICE TUMOR MODEL	PROTOCOL	PMID
ODN1668	Colon Cancer <b>Application:</b> Blockade of TNFR2 signaling enhances the immunotherapeutic effect of CpG ODN in a mouse model of colon cancer	20 $\mu$ g ODN1668 in 0.1ml PBS. Intratumor injection.	29295954
ODN1585 ODN1826 ODN2395	Colon Peritoneal Metastases <b>Application:</b> Intraperitoneal injection of class A TLR9 agonist enhances anti-PD-1 immunotherapy in colorectal peritoneal metastases	5nmol/mice of ODNs. Intraperitoneal injection.	36278484
ODN M362	Hepatocellular Carcinoma <b>Application:</b> Phosphorothioate modification of the TLR9 ligand CpG ODN inhibits poly(I:C)-induced apoptosis of hepatocellular carcinoma by entry blockade	5 $\mu$ g/mice of ODN M362. Intratumoral injection.	25224571
ODN1585 ODN1668 ODN2395	Mammary Adenocarcinoma <b>Application:</b> Intratumoral co-injection of the poly I:C-derivative BO-112 and a STING agonist synergize to achieve local and distant anti-tumor efficacy	50 $\mu$ g/mice BO-112 and 50 $\mu$ g/mice ODNs. Intratumoral injection.	34824158
ODN1585 ODN1826 ODN2395	Melanoma, Colon Adenocarcinoma <b>Application:</b> Nanoparticle delivery of immunostimulatory oligonucleotides enhances response to checkpoint inhibitor therapeutics	2nmol ODN1826 encapsulated within PEGylated TPNCs. Intravenous injection.	32493746
ODN2006 VacciGrade™, ODN2216 ODN M362	Breast Cancer <b>Application:</b> Oligodeoxynucleotides ODN 2006 and M362 Exert Potent Adjuvant Effect through TLR-9/-6 Synergy to Exaggerate Mammaglobin-A Peptide Specific Cytotoxic CD8+T Lymphocyte Responses against Breast Cancer Cells	100 $\mu$ g/mice MamA2.1 peptide and 100 $\mu$ g/mice ODNs. Intraperitoneal injection.	31091800

### VacciGrade™

InvivoGen exclusively provides choices of CpG ODNs of VacciGrade™.

VacciGrade™ is a high-quality pre-clinical grade. CpG ODN VacciGrade™ products are filter-sterilized (0.2 $\mu$ m) and filled under strict aseptic conditions in a clean room. The absence of bacterial contamination is assessed by a sterility test using a pharmacopeia-derived assay. The level of bacterial contaminants (endotoxins and lipoproteins) in each lot is verified using a LAL assay and/or a TLR2 and TLR4 reporter assay.

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## Protocol in Animal Models of Infectious Diseases

PRODUCT	AMINAL	PATHOGEN	PROTOCOL	PMID	
ODN 1585, ODN 1826, ODN 2395, ODN 2088	Mice	HSV-1	50µg/mice of either ODNs. Intranasal administration.	23043942	
<b>Application:</b> Modulation of TLR9 response in a mouse model of herpes simplex virus encephalitis					
ODN 2395	Mice	Influenza	20ng/ml ODN2395 and 10ng/ml Pam2CSK4. Aerosol delivery for 30 min driven by 10L/min air supplemented.	22299046	
<b>Application:</b> Synergistic TLR2/6 and TLR9 Activation Protects Mice against Lethal Influenza Pneumonia					
ODN1585, ODN1826, ODN2395	Mice	EHV-1	5µg/mice of ODNs. Intranasally administration.	31247247	
<b>Application:</b> Intranasal treatment with CpG-B oligodeoxynucleotides protects CBA mice from lethal equine herpesvirus 1 challenge by an innate immune response					
ODN1826, ODN1585	Mice	Sublethal Rickettsial	50µg/mice ODNs. Intravenous injection.	22470514	
<b>Application:</b> Systemic Treatment with CpG-B after Sublethal Rickettsial Infection Induces Mouse Death through Indoleamine 2,3-Dioxygenase (IDO)					
ODN2216	Cotton rat	Measles Virus	100µg/rat mixture of poly(I:C) and ODN 2216 (1:1). Subcutaneous injection.	24262312	
<b>Application:</b> Synergistic induction of interferon $\alpha$ through TLR-3 and TLR-9 agonists stimulates immune responses against measles virus in neonatal cotton rats					
ODN 2007	Chicken	AIV H9N2	15µg inactivated H9N2 virus, 2-10µg ODN2007 and/or 0.4-2µg Flagellin. Intramuscular injection.	30222508	
	<b>Application:</b> A Comparison of Toll-Like Receptor 5 and 21 Ligands as Adjuvants for a Formaldehyde Inactivated H9N2 Avian Influenza Virus Vaccine in Chickens				
	Chicken	AIV H9N2	10-50µg ODN2007. Intramuscular injection.	36680279	
	<b>Application:</b> Determining the Protective Efficacy of Toll-Like Receptor Ligands to Minimize H9N2 Avian Influenza Virus Transmission in Chickens				
	Chicken	AIV H9N2	15µg BPL inactivated H9N2 virus and 2µg ODN2007. Intramuscular injection.	29970157	
	<b>Application:</b> Induction of immune response in chickens primed in ovo with an inactivated H9N2 avian influenza virus vaccine				
	Chicken	AIV H6N1, Bronchitis Virus	4µg ODN2007 encapsulated in PLGA nanoparticles. Subcutaneous injection.	32494131	
	<b>Application:</b> Induction of Robust Immune Responses by CpG-ODN-Loaded Hollow Polymeric Nanoparticles for Antiviral and Vaccine Applications in Chickens				
	Chicken	Fowl Cholera	100µg rOmpH and 10µg ODN2007 in total 100µl. Intranasal administration.	28421815	
	<b>Application:</b> Cross-protection conferred by immunization with an rOmpH-based intranasal fowl cholera vaccine				
Ferrets	Nipah Virus	4-100µg HeVsG, 100µg-2.5mg aluminium ion, and 150µg ODN2007. Subcutaneous injection.	23867060		
<b>Application:</b> Vaccination of ferrets with a recombinant G glycoprotein subunit vaccine provides protection against Nipah virus disease for over 12 months					
Ferrets	Hendra Virus	4-100µg HeVsG, 100µg-2.5mg aluminium ion, and 150µg ODN2007. Subcutaneous injection.	21689706		
<b>Application:</b> A recombinant Hendra virus G glycoprotein-based subunit vaccine protects ferrets from lethal Hendra virus challenge					

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## Protocol in Animal Models of Other Diseases

PRODUCTD	DISEASE MODEL	PROTOCOL	PMID
ODN 1826	Ischemic Brain Injury	20 and 40µg/mice ODN1826. Intraperitoneal injection.	32510041
	<b>Application:</b> Preconditioning with CpG-ODN1826 reduces ischemic brain injury in young male mice: a replication study		
ODN 2006, ODN 1826	Atherosclerosis	2.5 - 120µg/mice ODN1826. Intravenous injection and subcutaneous injection.	26751387
	<b>Application:</b> Proinflammatory Stimulation of Toll-Like Receptor 9 with High Dose CpG ODN 1826 Impairs Endothelial Regeneration and Promotes Atherosclerosis in Mice		
ODN 1668	Heart Failure	60µg/mice of ODN1668. Intraperitoneal injection.	31312759
	<b>Application:</b> Administration of a TLR9 Inhibitor Attenuates the Development and Progression of Heart Failure in Mice		
ODN 1585	Lupus	2.5µg/mice of ODN1585. Intravenous injection.	28003376
	<b>Application:</b> Selective IRAK4 Inhibition Attenuates Disease in Murine Lupus Models and Demonstrates Steroid Sparing Activity		
ODN 2088	Type 1 Diabetes	10µg/mice of ODN2088. Intraperitoneal injection.	30094467
	<b>Application:</b> Toll-like receptor 9 negatively regulates pancreatic islet beta cell growth and function in a mouse model of type 1 diabetes		
ODN 2395	Insulin Resistance	2 ½g/mice of ODN2395. Intraperitoneal injection.	27373163
	<b>Application:</b> Nucleic Acid-Targeting Pathways Promote Inflammation in Obesity-Related Insulin Resistance		
ODN 1585, ODN 1668, ODN 1826, ODN M362	Peanut Allergy	As treatment: 0.5mg peanut protein and ODNs. Intraperitoneal injection.	23386314
	<b>Application:</b> Type B CpG oligodeoxynucleotides induce Th1 responses to peanut antigens: Modulation of sensitization and utility in a truncated immunotherapy regimen in mice		
ODN1585	Senscent T Cells	200-300µg CD153-KLH peptide and 10µg ODN1585. Subcutaneous injection.	32424156
	<b>Application:</b> The CD153 vaccine is a senotherapeutic option for preventing the accumulation of senescent T cells in mice		
ODN1668, ODN1585	Acute Lung Injury	51µg/mice ODNs. Intraperitoneal injection.	21844380
	<b>Application:</b> Nucleic acid-binding polymers as anti-inflammatory agents		
ODN1585	Acute Kidney Injury	620nmol/kg ODN1585. Intraperitoneal injection.	36586274
	<b>Application:</b> The potential biomarker TIFA regulates pyroptosis in sepsis-induced acute kidney injury		
ODN1585	Atherosclerosis	25µg/mice ODN 1585. Intraperitoneal injection.	26183767
	<b>Application:</b> CD4+CXCR3+ T cells and plasmacytoid dendritic cells drive accelerated atherosclerosis associated with systemic lupus erythematosus		

### RELATED PRODUCTS

Class A CpG ODNs:

ODN 2216 (Cat Code: tlr-2216)

ODN 1585 (Cat Code: tlr-1585)

Class B CpG ODNs:

ODN 1668 (Cat Code: tlr-1668)

ODN 2006 (Cat Code: tlr-2006)

ODN 2006 VacciGrade™ (Cat Code: vac-2006-1)

ODN 2007 (Cat Code: tlr-2007)

ODN 1826 (Cat Code: tlr-1826)

Class C CpG ODNs:

ODN 2395 (Cat Code: tlr-2395)

ODN M362 (Cat Code: tlr-m362)

TLR9 Antagonist:

ODN 2088 (Cat Code: tlr-2088)

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## CpG ODN 1018 VacciGrade™ **NEW**

CpG ODN 1018, also known as CpG 1018® or 1018 ISS, is currently the **ONLY FDA-approved CpG-based adjuvant** for human vaccine use[1]. ODN 1018 has been extensively tested in the clinic for its efficacious immunological effects, such as the production of IL-12, IL-18, and IFN-γ from macrophages and natural killer (NK) cells, promoting Th1 responses, and its involvement in antibody production and B cell proliferation[2].

It is a component of several approved vaccines, including the licensed hepatitis B virus vaccine HEPLISAV-B®[3]. Various pre-clinical and clinical trials are ongoing using ODN 1018 alone or together with alum in vaccine strategies against infectious diseases (e.g. SARS-CoV-2, pertussis) or cancer[4-6]. ODNs have been extensively tested for their potential to stimulate the clearance of amyloid pathology and treat Alzheimer's disease (AD)[7]. Clinical trials are ongoing investigating the impact of CpG 1018® alone in early AD patients[8].

InvivoGen provides **ODN 1018 VacciGrade™\*** with high-quality pre-clinical grade suitable for *in vivo* use. The absence of bacterial contamination (lipoproteins and endotoxins) has been confirmed.

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### **Influenza Virus Infection[4]**

Mice were primed and boosted intramuscularly (with a 3-week interval) with 3μg antigens and 3μg ODN 1018. 6 weeks after the prime, mice were intranasally challenged with 10x the 50% mouse lethal dose of the virus.

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### **Whooping Cough (Pertussis)[5]**

Mice were administered 50μl of vaccine intramuscularly, containing antigens (1/10-1/80 of human dose) and 10μg ODN 1018. Mice were boosted with the same vaccine formulations after 21d of the prime.

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### **Mesothelioma[9]**

Mice were peritumorally injected with 50μl endotoxin-free vaccine (50μg plasmid expressing CD40L, 25μg poly(I:C), and 25μg ODN 1018). The injections were repeated every other day for five doses.

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## **Therapeutic Role of Free CpG ODNs**

As potent activator of both innate and specific immunity, CpG ODNs drive the immune response towards the Th1 phenotypes[10]. By stimulating endosomal TLR9 to trigger the immune cascade, CpG ODNs were explored its potency in the treatment of cancers, allergies, and infectious diseases[7].

Pre-treatment of mice with ODNs before injection increased the survival rate of HSV-1 infection, while the treatment of ODNs after infection can also contribute to control the inflammatory response[11]. CpG ODN 2006 was extensively explored as anti-tumor agent in the clinic, including cutaneous T-cell lymphoma, melanoma, and in renal cell carcinoma[12].

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### **Herpes Simplex Virus Encephalitis(HSE)[11]**

The Pre-infection Studies: Mice were pre-treated with a single intranasal dose of 50 lg/mouse of either **ligands (Poly(I:C), ODN 1585, ODN 1826, ODN 2395, ODN 2088)** in a volume of 20μl of vehicle (0.9% saline). Then pre-treated mice were infected intranasally one day later with 3800 PFUs of HSV-1 (herpes simplex virus type 1). Mice were sacrificed on day 3, 4, and 5 post-infection.

The Post-infection Studies: Mice received the same treatment of **ligands (Poly(I:C), ODN 1585, ODN 1826, ODN 2395, ODN 2088)** 3 days following the infection with HSV-1 (4200 PFUs). Mice were sacrificed on day 3, 4, and 5 post-infection.

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## Colon Cancer[13]

Mice were intraperitoneally injected with 100µg antibodies or mouse IgG1 in 0.2ml PBS at days 1, 5, and 9. At days 2 and 4, 20µg **ODN1668 VacciGrade™\*** in 0.1ml PBS was intratumorally treated to the mice. One day after the last treatment, mice were sacrificed for harvesting tumor and lymphoid tissues.

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## Alzheimer's Disease (AD)[7]

Aged monkeys were subcutaneously injected with 2mg/kg ODN 2006 (a month interval) for 24-month period. All injections were administered at 8-9 a.m. before the monkeys were fed.

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## Combination Therapy of CpG ODNs

The combination of the antigen and CpG ODNs as adjuvant can lead to better therapeutic antigen-specific immune response, which are 5 to 500-fold greater than separate administration[10]. Combination of CpG ODNs with varied therapeutic strategies, such as monoclonal antibody therapy and chemotherapy were studied in animal models. The therapeutic efficacy in the current study was proven to be promising.[12].

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## Lethal Influenza Pneumonia[14]

Treatments were aerosolized to the animals for 30 min from a nebulizer driven by 10 L/min air supplemented. The following concentrations were used in the nebulizer reservoir: **Pam2CSK4** 10 µg/ml; **poly(I:C)** 100 µg/ml; **ODN2395** 20 µg/ml. Ligand concentrations in the airway lining fluid are calculated to be **Pam2CSK4** 10ng/ml; **poly(I:C)** 100ng/ml; **ODN2395** 20ng/ml.

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## Avian Influenza Virus (AIV)[15]

Chickens were vaccinated via intramuscular injection in the thigh muscle on days 7 and 21 post-hatch receiving 100 mL and 200 mL total volume, respectively. Chickens received 15 mg of formaldehyde inactivated H9N2 virus (around 960 HA units) per vaccination. Mixed with the inactivated H9N2 virus, chickens received either a high or low dose of **FLA-ST Ultrapure\*** or **CpG ODN 2007**, a combination of both, or **AddaVax**. Serum and lachrymal secretions were collected from chickens weekly beginning 7 days post-primary vaccination (ppv) and ending 28 days ppv.

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## Breast Cancer[16]

Mice was injected with 100 µg/mice of endotoxin-free antigen into the peritoneal cavity with or without the **ODN2006**, **ODN2216**, **ODN M362** (100 µg/mice for a given ODN type).

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## Novel Delivery System of CpG ODNs

To improve the stability, pharmacokinetic, and biodistribution, novel delivery system like nanoparticles, multi-component nanorods, and liposomes are developed[10].

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## Delivered by PEGylated Nanoparticles[17]

For intratumoral administration of immunostimulants, 0.2nmol of **ODNs (ODN1585, ODN1826, ODN2395 and their controls)** encapsulated within nanoparticles or unencapsulated were injected intratumorally at various time points. For intravenous therapeutic administration experiments, 1nmol of **ODNs** encapsulated within PEGylated nanoparticles or unencapsulated, in 150µL of PBS were injected into the lateral tail vein at various time points.

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## Delivered by Alginate Coated Chitosan Nanoparticles[18]

The vaccine contains suspension of alginate coated chitosan nanoparticles loaded with 10µg antigen and 10µg of the ODN1826 as adjuvant. 3 boosts within three weeks between each was administered in nasal mucosa. Four weeks after the final boost, mice were sacrificed.

## Mannose and CpG-ODN Coated Liposome Delivery[19]

The liposomal vaccine was assembled by DC-targeting mannose and ODN 1826 on the surface of liposome loaded with anti-tumor agent. Mice were injected with 2µg assembled liposome in 100µl PBS on days 6, 9, 12, and 15 after the tumor implantation.

## REMARKS

All the CpG ODNs in the reference and products marked as red are provided by **InvivoGen**. These data were generated on the basis of InvivoGen CpG ODNs potency that may not apply to other supplier lower quality CpG ODNs due to the known impact of TLR2 cross contamination or inaccurate batch to batch endotoxin level assessment.

\*The marked products (ODN 1018 VacciGrade™, ODN1668 VacciGrade™, and FLA-ST Ultrapure) are exclusively provided by InvivoGen, as VacciGrade™ and Ultrapure grade.

## RELATED PRODUCTS

ODN 1018 VacciGrade™ (Cat Code: vac-1018-1)  
Poly(I:C) LMW (Cat Code: tlr1-picw)

Pam2CSK4 (Cat Code: tlr1-pm2s-1)  
FLA-ST Ultrapure (Cat Code: tlr1-epstfla)

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