Local application of human IgG to prevent biomaterial-centered bacterial infection
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Chapter 1

Introduction and research objectives

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History of immunotherapy

In the 1890s, researchers first determined the efficacy of passively administered antibodies against pneumococcal infections in animals. This observation led scientists to vaccinate animals and use the resulting anti-sera to treat tetanus, diphtheria, rabies or vaccinia.\textsuperscript{4,16,26,29,46} Hericourt examined the protective capabilities of serum therapy by raising “specific” antibodies in animals to treat people with certain forms of cancer. While a short-term remission was realized, this was not yet a radical anti-cancer therapy, although results suggested that antibody therapy could be an important adjuvant therapy following surgery to prevent infection and therefore promote healing.\textsuperscript{25}

Just prior to World War I, pneumococcal pneumonia was epidemiologically the single most important infectious disease. The development of anti-pneumococcal sera received considerable attention and, by the early 1930s, became the standard treatment for lobar pneumonia.\textsuperscript{8} Immediate adverse reactions of serum therapy were fevers and chills, while more delayed, severe reactions referred to as “serum sickness” included rash, proteinuria and arthralgia.\textsuperscript{9} These problematic side-effects could be reduced by using human sera instead of sera raised in animals. In the treatment of measles, for example, even less severe reactions could be avoided by concentrating the protective elements comprising sera using ammonium sulfate precipitation\textsuperscript{32} and preparation of the immunoglobulin from pools of sera rather than serum from single donors.\textsuperscript{28} Development of a fractionation process for isolating purified immunoglobulin based on pH, ionic strength, temperature and cold ethanol fractionation (Cohn fractionation)\textsuperscript{11} set the stage for large scale fractionation of pooled sera and has constituted the basis for most modern preparations of commercial immunoglobulin ever since.

The first clinical use of these fractionated immunoglobulin products was in the prevention and mitigation of measles and as a prophylactic agent against hepatitis A via intramuscular injections. Later, gamma-globulin from donors with high titers against hepatitis B, rabies, tetanus, diphtheria and varicella-zoster was used for prophylaxis of these respective diseases.\textsuperscript{10,22} Immunoglobulin preparations for intramuscular use
(IMIG) produced by Cohn fractionation contained almost exclusively IgG with small amounts of IgM and IgA, but intravenous administration of this product gave rise to frequent and serious side effects resulting both from complement activation and also from dimeric forms of IgG. A number of different modifications to reduce IgM and IgA fractions and therewith the complement activation of the original product resulted in improved preparations for intravenous use (IVIG). The initial rationale for developing IVIG was the relatively low amount of IgG that could be administered intramuscularly due to pain at the injection site and limited muscle mass in some patients. Further therapeutic exploitation, however, has resulted in hundreds of clinical reports on IVIG treatment regimens and commercial product lines dedicated to specific IVIG formulations worth millions of dollars annually.

The immune system

The immune response system of humans and that of other higher animals provide mechanisms for specific responses to the invasion of pathogenic microorganisms and foreign materials. This response protects the host largely against disease. The immune response is characterized by specificity, memory and the acquired ability to detect foreign substances.

The specificity of this response allows for the recognition of even very slight biochemical differences between molecules. Consequently, the macromolecule coating on specific microbial strains can elicit a different response during infection than the macromolecules of even a very closely related strain of the same species. The immune response is adaptive and acquired: having responded once initial exposure of a particular recognized macromolecule, called an antigen, a memory system is established through cell communication that permits a rapid and specific secondary recognition response upon re-exposure to that same antigen. Because of this memory mechanism, humans can develop immunity against specific diseases and as a consequence, usually suffer from many diseases, like chicken pox, only once. To artificially acquire or prompt a state
of immunity, vaccines have been developed that intentionally expose the body to specific non-infective microbes, fragments, macromolecules, or other antigens, with the intent of generating immunity against the antigen upon repeated re-exposure. A well-known early example is vaccination by exposure to cowpox in the late eighteenth century by the English physician Edward Jenner, to prevent the acquisition of the deadly smallpox. Since that time, major world-wide vaccination efforts have eradicated many of the most deadly diseases. More advanced vaccination strategies are now being commercialized against many remaining infection problems.

Two forms of immunity

There are two different forms of mammalian immunity. The first, called antibody-mediated immunity, elicits cellular production of specific antibodies when foreign antigens are detected. Plasma cells derived from white blood cells (B-lymphocytes or ‘B-cells’) synthesize antibodies in response to the detection of foreign macromolecules with antigenic properties. This type of immunity is called humoral immunity, because after release by the B-cells, the antibody molecules circulate extracellularly through the body fluids. The second form of immune response is cell-mediated immunity, whereby certain cells of the body acquire the ability to destroy other cells that are recognized as foreign or abnormal. This type of immunity depends upon T-lymphocytes or ‘T-cells’.

Both B- and T-cells originate from the bone marrow and become differentiated during maturation. Precursors for T-cells pass through the body to get processed in the thymus gland, located apical to the heart. They remain mostly inactive until fully matured in other lymphoid tissues. B-lymphocytes also develop in the bone marrow but the name ‘B-cell’ refers to bursa-dependent lymphocytes because, in birds and chickens, these cells differentiate in the bursa of Fabricius before starting to produce antibodies. Humans do not have a bursa of Fabricius; the designation B-lymphocyte is applied to lymphocytes that can differentiate into antibody-synthesizing cells in humans. Once stimulated by antigenic recognition, these B-cells generate antibody-secreting plasma cells that produce a variety of classes of antibodies that collectively are called immunoglobulins.
To effectively battle foreign antigens and infection, the immune system is equipped with a complex immunological tolerance mechanism. The most important aspect is host self-tolerance that prevents the body from mounting an immune attack against its own tissues. Since the immune system randomly generates a vast diversity of antigen-specific antibodies over time, a potential risk exists for such an attack that has to be prevented incrementally by self-check processes over a lifetime rather than being genetically pre-programmed. Next to the basic structures of macromolecules that elicit antigenic “foreign” recognition responses, other factors including the time and the site of encountering epitopes are also important in building host tolerance. For example, in one tolerance process, B-cells that express surface receptors with high binding affinity for self membrane-bound antigens are deleted immediately after leaving the bone marrow to prevent an auto-immune attack on host tissues.

**Antibody molecules as immunoglobulins**

Antibody molecules or immunoglobulins comprise a large mass fraction of circulating, soluble proteins found in the serum (26mg/ml) of the blood, extravascular fluids, mucosal membranes, and some tissue surfaces. Synthesis of antibodies in B-cells or plasma cells occurs after antigenic stimulation. Five different classes of antibodies can be produced: IgG, IgA, IgM, IgD and IgE. The various classes serve different functions in host immune response with their basic properties outlined in Table 1.

All immunoglobulin molecules have the same basic structure consisting of four peptide chains, two identical heavy chains and two identical light chains, joined by multiple disulfide bridges linking the chains and stabilizing the tertiary and quaternary protein structure eliciting function (Figure 1). Differences in the heavy chains are responsible for the five major classes of immunoglobulins. The light chains always comprise kappa (κ) and lambda (λ) peptide sub-units that allow the immune system to combine atorially endless arrays of different versions of immunoglobulin binding sites capable of recognizing encountered antigens.
<table>
<thead>
<tr>
<th>Property</th>
<th>IgG</th>
<th>IgA</th>
<th>IgM</th>
<th>IgD</th>
<th>IgE</th>
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<tbody>
<tr>
<td>Molecular weight</td>
<td>$1.50 \times 10^5$</td>
<td>$1.62 \times 10^5$</td>
<td>$9.50 \times 10^5$</td>
<td>$1.85 \times 10^5$</td>
<td>$2.00 \times 10^5$</td>
</tr>
<tr>
<td>Heavy chain</td>
<td>$\gamma$</td>
<td>$\alpha$</td>
<td>$\mu$</td>
<td>$\delta$</td>
<td>$\epsilon$</td>
</tr>
<tr>
<td>Light chains</td>
<td>$\kappa$ or $\lambda$</td>
<td>$\kappa + \lambda$</td>
<td>$\kappa + \lambda$</td>
<td>$\kappa + \lambda$</td>
<td>$\kappa + \lambda$</td>
</tr>
<tr>
<td>Valency for antigen binding</td>
<td>2</td>
<td>2 (4)</td>
<td>5 (10)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Concentration in Normal serum</td>
<td>8-16mg/ml</td>
<td>1.4-4mg/ml</td>
<td>0.5-2mg/ml</td>
<td>0-0.4mg/ml</td>
<td>17-450µg/ml</td>
</tr>
<tr>
<td>% total immunoglobulins</td>
<td>70-75</td>
<td>15</td>
<td>10</td>
<td>0-1</td>
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<td>Complement fixation</td>
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<td>+++</td>
<td>-</td>
<td>-</td>
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<td>Classical:</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alternative:</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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<td>Cross placenta</td>
<td>+</td>
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<td>-</td>
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<td>Fix to mast cells</td>
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<td>-</td>
<td>+</td>
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<td>Macrophage/neutrophil binding</td>
<td>+</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Major characteristics</td>
<td>Most abundant Ig in body fluids; combats infecting bacteria and toxins</td>
<td>Major Ig in sero-mucous secretions: protects external body surfaces</td>
<td>Effective agglutinator produced in early immune response</td>
<td>Mostly present on lymphocyte surfaces</td>
<td>Protects external body surfaces; responsible for atopic allergies</td>
</tr>
</tbody>
</table>

**Table 1:**
Properties of the five classes of immunoglobulins

**Figure 1:**
General structure of an immunoglobulin unit: two heavy chains (50,000Da) and two light chains (25,000 Da) arranged in a Y-shape, stabilized by multiple disulfide bonds.
Either of the light chain types may combine with any of the heavy chain types, but in any one immunoglobulin molecule, both light chains are identical, as are the heavy chains. This allows the antibody to bind simultaneously with both ‘arms’ bivalently to antigens. This important bivalent function permits antigen cross-linking, ultimately leading to immunoprecipitation, membrane patching, capping, signaling and subsequent complement activation to neutralize the antigenic entity.\textsuperscript{24}

The fundamental basis of antibody-mediated or humoral immunity is derived from the reactions of antigen with antibody molecules. The interactions of antibodies with surface antigens of bacterial cell walls render many pathogenic bacteria susceptible to phagocytosis and cell based enzymatic destruction (neutralization). Many ingestive processes (e.g., bacteria, latex or polystyrene particles, etc.) require antigen-antibody reactions before phagocytic engulfment can take place. This facilitating process, activated by antigen-antibody reactions, is called opsonization. This process can be initiated by non-specific antibody-binding but for many pathogenic, virulent organisms, opsonization can only be established by specific antibodies with Fab fragments directed against characteristic epitopes on the bacterium surface.\textsuperscript{1,2,17,45} Destruction of these pathogens inherently resistant to opsonophagocytosis --especially those armed with a polysaccharide protective capsule-- requires antigen-antibody reactions to overcome and prevent severe infections. The Fc portion of the IgG molecule contains sites that are recognized by a class of cellular receptors called FcγR responsible for cell-mediated recognition of antibody-antigen complexes. These receptors are found primarily on polymorphonuclear cells (PMN’s), monocytes, macrophages and natural killer (NK) cells, and assist (along with C3b complement receptors) in the phagocytosis (clearance) of immune complexes and antibody-coated foreign substances like pathogenic bacteria. Once combined with an antigen, the Fc portion of the IgG molecule can also be recognized and bound by complement C1 to form an antigen-antibody-complement complex that activates the complement cascade, ultimately leading to pathogen lysis.

The immunoglobulin molecule can be split by the enzyme, papain, into Fab binding fragments (ab=antigen binding) and the Fc tail fragment (c=crystallizable or constant).
The enzyme, pepsin, cleaves immunoglobulins in another location forming divalent Fab fragments \([(\text{Fab})'_2]\) but not yielding Fc fragments. The structural subunit flexibility and compositional variability of the immunoglobulin molecules permit the specificity of their reactions with antigens and signaling to cellular immune elements (e.g., T-cells, NK cells). Additionally, allosteric changes in immunoglobulins result in a three-dimensional conformation that allows the antigen- and antibody molecules to fit properly together after an “adapted fit” model. The Fab regions are hypervariable, allowing for diversity of antibody molecules that provide the necessary basis for wide, protective immune response against many different antigens, including bacterial toxins, together with the infinite different structural variations resulting from genetic variation.

**Immunoglobulin G - IgG**

IgG is the largest mass fraction of the body’s soluble immunoglobulin molecules, comprising generally 70-75 percent of total antibody circulating mass.

Research described in this dissertation is focused on the local delivery of immunoglobulin G to prevent bacterial infection, a characteristic property of IgG discovered around 1900. Reviewing the capabilities of other immunoglobulin classes or cellular immunity is beyond the scope of this study and will therefore not be addressed in further detail.

The IgG immunoglobulin group consists of four protein subclasses all sharing the common structure shown in Figure 1 (IgG₁, IgG₂, IgG₃ and IgG₄), with IgG₁ being the largest fraction (~65%). The different subclasses vary slightly in chain composition, number and arrangement of their disulfide bonds and function. IgG₂ antibodies are opsonic and are produced in the human body in active response against pathogen toxins. IgG₁ and IgG₃ antibodies activate complement most effectively and bind best to monocytes and macrophages to induce phagocytosis of opsonized bacteria. IgG₄ antibodies function as skin-sensitizing immunoglobulins.
Stimulated by chemoattractants in peripheral tissues, IgG can pass readily through the vascular endothelium into the extravascular, extracellular spaces (extravasation) where it can react with antigens to stimulate the attraction of phagocytic cells to invading microorganisms. IgG reactions with surface antigens on bacteria also activate the complement system and attract additional neutrophils to the site of infection. IgG is also the only immunoglobulin that passes through the placenta to confer passive immunity to the fetus and neonate.

**Current IgG clinical preparations**

**Safety**

Currently, intravenous IgG (IVIG) is used in millions of doses annually to treat many specific pathologies in immunocompromised patients, resulting from immune-depleting therapies or diseases. IVIG is produced from pools of purified human IgG collected from thousands of donors. Depending upon the population from which the plasma is derived, IgG titers against different pathogens vary. To ensure the quality of the product to treat infection, titers against a number of different bacterial, viral and fungal antigens are usually determined. Four recent seminal reviews written within this decade have focused on most of the important issues (clinical and economic) surrounding the use of IgG to treat various infectious pathologies.\(^{7-9,22}\) The consensus view of IVIG from these reviews is summarized below:

For many years, Cohn fractionation was thought sufficient to eliminate viral contamination in IgG clinical preparations. Although this was proven true in 1986 for HIV by both the Food and Drug Administration (FDA) and the Centers for Disease Control (CDC), transmission of hepatitis B was still regarded as possible. A 1996 study of the aggregated risk of viral transfer (HIV, HBV, HCV and HTLV) in all donor blood products available (e.g., blood, plasma, immunoglobulins, clotting factors) was one in 34,000 per unit transfused.\(^{27}\) Individual donors are therefore screened for the presence of HbsAg (hepatitis B surface antigen) in their blood to eliminate viral spread.
Unfortunately, hepatitis C (non-A, non-B hepatitis) screening was also required since outbreaks of this disease occurred both among immune thrombocytopenic purpura patients (ITP) and immunocompromised individuals who received IVIG preparations.\textsuperscript{14} All currently available evidence indicates that the new solvent/detergent (SD) treatment eliminates the risk of transmission of the major pathogenic viruses in blood --HIV, HBV and HCV-- as well as other enveloped viruses.\textsuperscript{27} Between 1985 and 1997, the New York Blood Center recorded the administration for the US of approximately 5,790,000 doses of SD treated IMIG-IVIG (≈28,951,000g IgG), excluding anti-D IgG (1,000,000 doses), HB-IgG (117,000 doses), CMV-Ig (121,000 doses), RSV-Ig (199,000 doses) and other Ig products (anti-tetanus etc., 486,000 doses) without reported toxicities. Even SD-treated plasma from HIV-infected men, pooled to produce hyper-immune anti-HIV immunoglobulin preparations, did not transmit HIV or hepatitis and the immunoglobulin has now been proven to be safe in clinical trials.\textsuperscript{14,27} There is a significant difference in the patterns of clinical use of human polyclonal IgG between the United States and Europe where IgG use is significantly less attributed in part to the patient paranoia and commercial stigma of blood-derived products. Unfortunately, European blood-banks are not sharing their data with third parties about the use of IgG which makes a direct comparison between the two continents impossible (personal communication Dr. van Aken, CLB Amsterdam, The Netherlands).

\textit{Efficacy}

The therapeutic efficacy of IVIG has been studied against a number of viral diseases including HIV, herpes simplex, Epstein Barr virus (EBV) and varicella zoster. Viral disease occurs by viral particles that successfully enter (transfect) a host-cell, multiply using the host replicating machinery, lyse the host cell and disperse to invade other host cells. Specific IgG antibodies neutralize viruses by attaching to viral particles and preventing the viral transfection processes by inhibiting the virus to enter the host-cell. In this case, the viral binding titer of IgG can approximate the neutralization titer, since IgG-virus complexation limits infectivity.
Although numerous animal data suggest that viral illness can be modified with passive immunization,\textsuperscript{19,34,36,37} the best human results have shown that only some symptomatic improvement is achieved, or that viral shedding was reduced.\textsuperscript{39}

In January 1996, a specific respiratory syncytial virus immune globulin intravenous (human) (RSV-IGIV) product (RespiGam®, Medimmune, Inc., Gaithersburg MD) was introduced to the United States clinical market. This originally IVIG product pooled from vaccinated, hyperimmune human donors, contains a high concentration of neutralizing and protective antibodies directed against RSV,\textsuperscript{38} the main cause of severe sinusitis and pneumonia in young children. Clinical studies have been successful in proving this product’s efficacy as being the first anti-viral immunoglobulin product.\textsuperscript{21}

The rationale for using IVIG against bacterial infection is just as compelling as its use against viruses. Supplementing broad spectrum immunoglobulins will supply a patient with sufficient opsonic antibodies to fight present and potentially pathogenic bacteria. IVIG is reported to synergize with $\beta$-lactam antibiotics since IVIG contains anti-lactamase antibodies against antibiotic resistant pathogens.\textsuperscript{13} Although encouraging results from randomized blinded studies, especially in newborns and intensive-care patients, were achieved with IVIG,\textsuperscript{5,12,18,23,39-41} antibody therapy is currently only indicated in relatively few clinical infection situations. Chemically produced antibiotic formulations have proven over the years to be more efficacious, less expensive and more versatile. Only in situations where immunoglobulin-deficient patients are involved or post-exposure prophylaxis is needed against different viruses (e.g., rabies, measles, hepatitis A and B, varicella) including toxin neutralization (diphtheria, tetanus, botulism), can IVIG provide measurable benefit.

Additionally, IVIG treatment is very expensive for several reasons. First, IVIG requires intravenous infusion and hospitalization, unlike other, simpler, effective antibacterial products that have been on the market for decades (e.g., oral antibiotics). Secondly, many antibiotics are now off patent, and can be produced inexpensively under a generic name, while the cost of IVIG treatment has increased due to a current world-wide
shortage of donated blood, and enhanced screening and safety requirements in its preparation from serum. The price for one vial of IgG (10 grams; one dose) in 1994 averaged approximately $300 while the manufacturer for the same vial in April, 1999, charged roughly $900 (Baxter Healthcare). Because of the still unproven clinical efficacy when applied intravenously, high cost, low availability and associated stigma as a blood-derived product, IVIG has not competed well against antibiotics.

However, in the prevention and treatment of infections in contaminated wounds (e.g., abdominal surgery, burns, traumatology) the use of broad-spectrum protective agents provide a major advantage that remains attractive. This has been the rationale supporting the use of broad-spectrum antibiotics as prophylaxis and as first-line of defense to treat these infections (e.g., penicillin, later cephalosporins). Unfortunately, widespread antibiotic resistance, the emergence of new pathogens and the increase in immunocompromised patients leaves many anti-microbial drugs less effective than ever before.

Also, the increased use of biomaterial implants and their propensity to promote the formation of an overlying glycocalix by adhering microorganisms (=biofilm-forming infections) call for the development of new anti-infective strategies in the race against virulent and therapy-resistant bacteria. By reducing bacterial adhesion to a biomaterial implant during surgical intervention and therewith reducing the risk for biofilm formation, host tissue integration of the implant could be increased. Improved tissue integration and wound healing, not complicated by immediate postoperative wound infection, are also important in the prevention of latent infections caused by hematogenous spread of bacteria that can enter the bloodstream during e.g., dental restoration procedures or a penetrating trauma and colonize the biomaterial even years after initial implantation. Neutralizing contaminating organisms intra-operatively before the 4-6h “decisive period” is over could bring reduction in postoperative, biomaterial centered infection with virulent (antibiotic-resistant) bacteria.
Non blood-derived, recombinant custom monoclonal antibodies (Mabs) are currently being improved for specific therapies, but highly specific preparations of Mabs are very expensive and are only slowly becoming more abundant and available for clinical application. The use of intravenous IVIG may be appropriate in some indications but continues to be both costly and scarce. Moreover, considerable variation between different lots of the same product can occur, and an in vitro titer may not correlate to an in vivo titer or neutralization or therapeutic efficacy, because of differing antibody affinity, epitope restriction and IgG subclass composition.

Since infectious complications leading to the dangerous state of septic shock frequently systemize from local infections (e.g., i.v. catheter, urinary tract infection (UTI), orthopaedic implant infection), local anti-infective therapy as an alternative to systemic antibiotic prophylaxis or treatment, applied directly to sites of infection could prove very useful. However, in the face of increasing antibiotic resistance, increased antibiotic use should be discouraged, especially in local applications that could encourage resistance. By potentiating the body’s own intrinsic ability to overcome bacterial invasion, preventing systemic spread of infection and the cause of sepsis, infection incidence could be reduced, ultimately leading to a reduction in antibiotic use and increasing antibiotic resistance. Several immuno-modulatory paths can be stimulated locally at infection sites to work in tandem with or without antibiotics. In particular, humoral immunopotentiation involves supplementation of antibodies using immunotherapy. Such an approach side-steps antibiotic resistance mechanisms since humoral immunity works by a distinctly different mechanism. Importantly, bacterial antibiotic resistance does not alter their susceptibility for opsonization and phagocytosis. Hence, immunotherapy using IgG should function just as well against resistant organisms. Since IVIG has demonstrated limited clinical appeal, a shift in the use of immunotherapy from systemic treatment to local application represents a new route to provide humoral immunopotentiation at sites of high infection risk. Such an approach could be effective using reduced IgG doses and sophisticated delivery strategies to reduce infection incidence, severity, and antibiotic resistance complications.
Research objectives

The primary aim of this thesis research is to investigate the efficacy of locally applied pooled polyclonal immunoglobulins (IgG) to prevent bacterial infection with different bacterial challenges in different in vitro and in vivo models.

Specifically, the hypothesis is that locally applied, pooled polyclonal IgG represents a useful prophylactic agent to prevent post-surgical bacterial infection by reducing bacterial adhesion and biofilm formation in the wound, and stimulating phagocytic clearance, ultimately leading to increased host survival.

This hypothesis was assessed using several experimental designs:

- First, an in vitro study was conducted using a parallel plate flow chamber to study the adhesion of Pseudomonas aeruginosa IFO3455 to glass in the presence and absence of IgG;
- Secondly, a closed murine peritonitis model was used to study the efficacy of locally applied IgG against P. aeruginosa IFO3455 and other clinically relevant bacteria that infect the abdominal cavity;
- Thirdly, in a newly developed animal model for investigating postoperative spinal implant infection, the anti-infective efficacy of locally applied IgG was tested against methicillin resistant Staphylococcus aureus (MRSA);
- Fourth, in both a murine burn- and a closed peritonitis model, IgG was applied locally together with systemic, prophylactic but sub-optimal doses of a third generation cephalosporin to study the additive or synergistic effects when IgG is administered in tandem with a currently clinically relevant antibiotic;
- Lastly, an open peritonitis implant model in mice was developed to study the efficacy of the local application of IgG in a controlled-release gel-carrier in tandem with systemic prophylactic cefazolin or vancomycin to prevent biomaterial-centered infection by MRSA and P. aeruginosa.
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