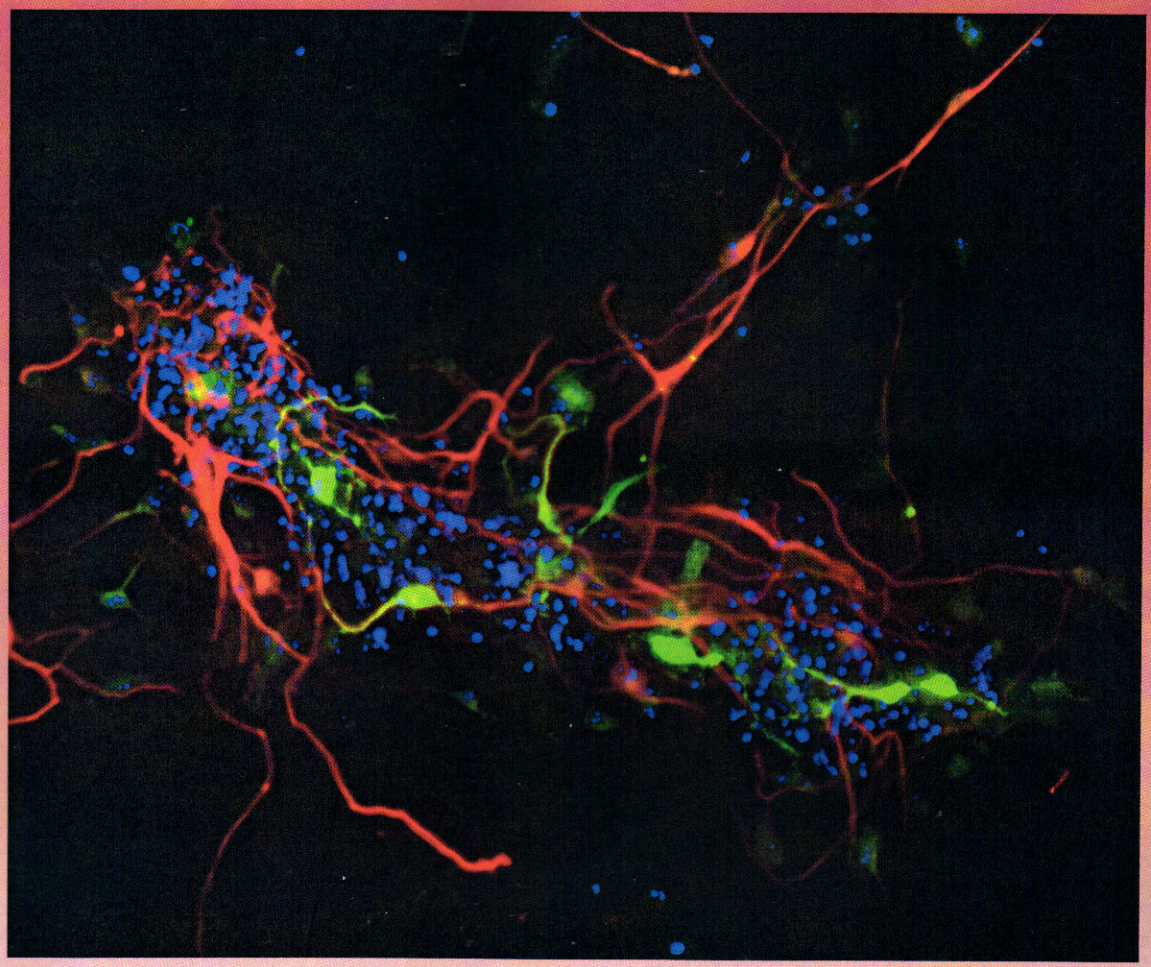
# Abstracts of the 2nd Joint Meeting of Pathology And Laboratory Diagnostics



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## HOST DEFENSE AND HOST PATHOGEN INTERACTIONS

### HDHP1. Analysis of Polymorphism C558T of *MAL* (*TIRAP*) in Mediterranean Spotted Fever

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**Background:** In our previous studies, we have demonstrated that cytokine polymorphisms, such as *IFN γ* +874T/A or *IL-17* SNP (7488T/C), might interfere with *R. Conorii* infection control. In addition, we have reported that +896A/G *TLR4* SNP is a component of a genetic background that might influence the clinical outcome of Boutonneuse fever (Mediterranean spotted fever, MSF). The +869G allele, that attenuates receptor signaling, was actually significantly overrepresented in symptomatic patients. Rickettsial PAMPS recognised through TLR4 and TLR2, activates the MyD-88 signaling pathway, which is involved in the transcription activation of pro-inflammatory cytokine genes. In this pathway MAL (also known as TIRAP) plays a crucial role, therefore, *TIRAP* polymorphisms may influence the response to the pathogen. In particular, we analyzed C558T of *TIRAP* that seems to attenuate TLR signaling.
**Methods:** A total of 70 Sicilian patients affected by MSF and 230 control subjects matched for age, gender, and geographic origin were typed for *TIRAP* SNP (C558T) according to our laboratory procedures.
**Results:** No significant differences between the two groups were observed; therefore, the *TIRAP* C558T genotypes seem not to influence the susceptibility or protection against MSF.
**Conclusions:** The results obtained suggest that the analyzed SNP on the gene coding for MAL does not seem relevant in determining increased susceptibility for the development of MSF. Nevertheless, it is appropriate to enlarge the casuistry and the number of SNPs involved in TLR signaling pathways to better define the genetic background that modulates the immune response against *R. conorii* infection and the consequential clinical outcome.

### HDHP2. Cytokine Polymorphisms and Susceptibility to Infectious Diseases

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**Background:** An individual's susceptibility to infection is determined by a variety of factors, such as pathogenicity of infecting microbes, and the effectiveness of the host's defense. An individual's genetic background affects the extent of inflammatory responses that, in some cases, might develop as SIRS and sepsis. Important candidate genes for host susceptibility to infection are genes coding for cytokines crucial for the host's primary response to infection.
**Methods:** A review of the literature from the last 15 years was performed.
**Results:** Literature review in some cases shows contradictory results. For *TNF*, G /A transition at -308 nt seems to influence the susceptibility, severity, or response to therapy in cerebral malaria, *Helicobacter pylori* and HCV infections. However, the -308A allele might be protective against cytomegalovirus infection. The 874TT *IFNG* genotype might be involved in susceptibility to Mediterranean spotted fever and an association of this genotype, starting from our seminal paper (Lio et al. 2002), to TBC infection seems to be well established, at least in Caucasians. Furthermore, high secretory genetic variants of interleukin-10, a natural modulator of inflammation, associated with susceptibility to severe meningococcal disease as well as to SIRS, has paradoxical contrasting effects during viral infections.
**Conclusions:** Review of the literature data clearly indicates that cytokine genetic background influences host response to infectious disease. However, the definition of cytokine SNPs as useful genetic markers will be reached only when analysis will identify all the relevant alleles in interacting cytokine functional pathways allowing risk stratification and modulation of infectious disease therapeutic managing at the individual level.

### HDHP3. Microbiota Regulation of Fungal Commensalism and Parasitism

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**Background:** The host immune system is considered one primary obstacle to fungal colonization. In the case of commensals, such as *Candida albicans*, the constant intertwining with the mammalian immune mechanisms would predict a contingency-based system during co-evolution to guarantee persistence in an inflammatory host environment. However, in concomitance with defects in the innate and adaptive immune systems or microbial dysbiosis, the fungus may shift from a state of commensalism to parasitism and can cause severe chronic mucosal infections. Recent progress in our understanding of how fungal signaling circuits operate molecularly in sensing environmental factors suggests that this process is much more complex than previously appreciated. It is now clear that a three-way interaction between host, fungi, and microbiota dictates the types of host-fungus relationship.
**Methods:** We have explored metagenomics for the purpose of deciphering the contribution of the microbiota to fungal commensalism and parasitism.
**Results:** By correlating changes in metabolite profiles with microbiota metagenomic composition, we have defined a functional node by which certain bacteria species contribute to host-fungal symbiosis and mucosal homeostasis in the gut.
**Conclusions:** The implications of our study are that studying the human gut microbiota in the trans-omics era, with a focus on metagenomics and metabonomics, is providing novel insight into the composition, function and evolution of our gut microbiota and mycobiota.
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### HDHP4. Elucidating the Molecular Mechanisms of *Mycobacterium avium* subsp. *paratuberculosis* Intracellular Survival

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**Background:** Johne's Disease (JD), a wasting disease of ruminants, is of major concern within the agricultural and food defense industries. The etiological agent of JD is *Mycobacterium avium* subsp. *paratuberculosis* (MAP). MAP evades host-mediated immune responses, forming an environmental niche that supports bacterial growth, 'containment' of the infection, and metabolic dormancy. The MAP genome is closely related to *Mycobacterium tuberculosis* (Mtb), the causative agent of tuberculosis disease, and has led to hypotheses on the contribution of various genes to MAP pathogenesis.
**Methods:** An analysis of MAP differential gene expression suggests *relA* and *irtAB* homologs as virulence factors. Further, a *relA* deficient MAP strain demonstrated survival attenuation *in vivo* and elicited an immune response that limited colonization by challenge with wild-type MAP. We hypothesize that MAP *relA* and *irtAB* genes contribute to pathogenesis and compared *in vitro* growth characteristics and epithelial cell invasion of wild-type MAP to strains harboring deletions in these genes.
**Results:** Our findings suggest a clear role for *RelA* in MAP growth.
**Conclusions:** Mechanisms underlying Mtb infection include the stringent response and iron acquisition. The stringent response is initiated by unfavorable environmental conditions and expression of the *relA* gene. Deleting *relA* in Mtb results in attenuation. During active growth, Mtb synthesizes carboxymycobactin, a secreted siderophore. The co-transcribed gene cluster *irtAB* has been characterized to function in iron transport from Fe-carboxymycobactin. Deletion of the *irtA* gene abrogates this transport mechanism. Findings report *RelA* gene is essential for growth.