ASM-JSC Joint Symposium “Topics in Microbiology and Chemotherapy”

司会のことば

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アメリカ微生物学会（ASM）は，現在，約 43,000 人の会員を擁しているが，その 1/3 は国外メンバーであることから，国際的な学術活動に積極的に取り組んでいる。2006 年 1 月に ASM 会長の Stanley Maloy 教授が第 17 回日本臨床微生物学会総会（岡田淳会長；横浜）の招聘講演で来日した際に，日本化学療法学会及び日本感染症学会の理事長を交えて日米間の将来の協力についての協議が行われ，機会があれば合同で学術集会を開催することとした。今般，第 57 回日本化学療法学会総会長の山口恵三教授のご好意により ASM-JSC 合同シンポジウムが開催されることとなり，ASM では演者として以下の 3 名の著名な研究者を派遣することを決定した。Bonomo 博士は優れた感染症医であると共に，β－ラクタマーゼの有機化学的・遺伝生化学的な研究で著名であり，2005 年より ICAAC のプログラム委員を勤めている。今回は，最近の研究テーマである多剤耐性 *Acinetobacter baumannii* の耐性機序を中心に，緑膿菌や肺炎桿菌の多剤耐性に関して最近の知見を解説し，多剤耐性菌による感染症への対応について論じると伝えてきている。Greenberg 教授は，1980 年代半ばから *Vibrio fischeri* の蛍光の autoinducer である acyl-homoserine lactone に関わる遺伝子 *luxI* の発現について一連の研究成果を報告している。ASM のシニア会員が構成する American Academy of Microbiology（AAM）の Board of Governor メンバーに選任されており，Cell-Cell Communication や Microbial Community 関連の会議の主催などの活躍を通じて，国際的な学術交流に貢献している。今回は，“sociomicrobiology”と題して，緑膿菌のビルレンスにおける quorum-sensing の関与と，緑膿菌感染症に対する anti-quorum-sensing 療法の可能性を論じると共に，細菌が集団として示す特異的な性状の一例として緑膿菌のバイオフィルムを取り上げ，その対応は新たな治療法の開発に繋がることを論じると伝えてきている。Calva 教授は，1980 年代半ばよりチフス菌の外膜タンパク OmpC の構造と機能及び遺伝子発現などの広範な研究を行ってきており，最近ではチフス菌のビルレンスに関わる複数の遺伝子の発現を制御する因子 LeuO の働きなどを報告している。国際的に活発な学術活動を続けてきており，AAM の International Member Committee の委員長を勤めている。今回は，ヒトおよび家畜由来の食物から分離されたサルモネラ菌の薬剤耐性に関して論じるとのことであり，国内でも鶏肉のサルモネラ菌汚染が問題となっているので，興味深い論議が行われることと期待される。ASM から派遣される上記の 3 名の著名な研究者の講演に対応して，JSC からは今回のシンポジウムの Moderator を勤める平松　啓一が“MRSA の逆襲”と題して，黄色ブドウ球菌が抗生物質の攻撃から身を守るための対応策“regulator mutations”による進化について，最近得られたゲノム情報に基づいて論じる。4 題の演題は講演要旨に記述されているように，何れも最新のデータに基づいて今日の化学療法における問題点を解析し，その対応策を思考するものであり，会員の方々からの活発な論議を導き出すものであると期待される。

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1. MDR in *Acinetobacter, Pseudomonas, and Klebsiella:* common themes and future trends

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Bonomo, Robert

This discussion will center upon the problem of antibiotic resistance (multidrug resistance, MDR) in *Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae.* Here we will summarize the rapidly expanding knowledge of resistance determinants in these problematic Gram negative pathogens and review available treatment options.

MDR *A. baumannii* are among the most resistant pathogens encounter the hospital environment. Resistance to β-lactams is mediated by β-lactamases (AmpC -type), efflux pumps, alterations in penicillin binding proteins, and changes in outer membrane proteins. Of these mechanisms, the primary concern is the presence of carbapenemases (OXA, MBL). Resistance to aminoglycosides is usually mediated by specific aminoglycoside modifying enzymes, efflux pumps, or by specific ribosomal methylases. Quinolone resistance arises by mutations in the gyrase enzymes or by efflux pumps. Taken together, the melding of these genes on to a specific resistance island poses unique challenges. In the case of *Pseudomonas*, the number of efflux pumps vastly contributes to the overall resistance phenotype. In addition, loss of permeability and biofilm formation contributes significantly to resistance. In *Klebsiellae*, the emergence of carbapenemases (KPC) and plasmid mediated quinolone resistance significantly adds to the MDR phenoytpe.

Novel agents such as doripenem and tigecycline are offered as alternatives to current antibiotics, but these are limited. The clinician now resorts to the use of colistin, rifampin and azithromycin as novel therapies. Novel combinations may offer hope in seriously ill patients . The future of effective therapy against MDR pathogens remains elusive.

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2. Sociomicrobiology : Communication and Coordination of Group Activities in Bacteria-A Target for Bacterial Virulence Therapeutics

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Greenberg, Peter

Until recently there was a long-held belief among biologists that social activities were by and large restricted to animals, and that creatures as small as bacteria would not benefit from sociality. Thus the laws that govern the evolution and behavior of animals would not all apply to bacteria. Over the past decade we learned that bacteria are social creatures. Not only does sociality apply in the microbial world but because bacteria are easily studied in the laboratory they are excellent models for understanding the biology of social behavior. The social activities of bacterial are often critical to their success as pathogens. We have learned that bacteria are capable of the most basic elements of sociality-communication and specialized activities within groups. The presentation will focus on one type of communication system that occurs in many Gram-negative bacteria, acyl-homoserine lactone quorum sensing using *Pseudomonas aeruginosa* as an example. *P. aeruginosa* controls the expression of hundreds of genes by a communication system that has become known as quorum sensing because it enables individuals in a population to take a census of their peers. Based on the information the group can coordinate their activity (gene expression-the quorum sensing response). The quorum-sensing response is critical for virulence of *P. aeruginosa* and there are efforts under way to develop anti-quorum-sensing therapeutics to treat *P. aeruginosa* infections. At the same time information on bacterial communication was accumulating, information on the ability of bacteria to form communities of physically interacting individuals was also accumulating. These communities called biofilms appear to exhibit division of labor, and special defense systems. This presentation will address ways in which we might translate basic research on biofilms into new therapies for chronic biofilm infections. Again, as with communication, *Pseudomonas aeruginosa* will be used as an example. This new view of a microbial world full of social activities has led not only to new approaches towards the treatment of bacterial infections, but also to biotechnology innovation.

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3. Association of virulence plasmid and antibiotic resistance determinants with chromosomal multilocus genotypes in Mexican *Salmonella enterica* serovar Typhimurium strains

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Salmonella enterica subspecies *enterica* serovar Typhimurium (*Salmonella* Typhimurium) is considered a broad host range serovar, usually associated with gastroenteritis in a broad range of phylogenetically unrelated host species. The aim of this study was to compare the genetic diversity of core and accessory genes of a *Salmonella* Typhimurium population isolated from food-animal (pork, beef and chicken) and human (with diarrhea, systemic infection and asymptomatic) sources in four regions of Mexico (from the Southeastern to the Northwestern part of Mexico). Multilocus sequence typing (MLST) and macrorestriction fingerprints by pulsed-field gel electrophoresis (PFGE) were used to address the core genetic variation. The presence of genes involved in antibiotic resistance carried in the *Salmonella* genome island (SGI1), integrons or the plasmid-borne betalactamase *cmy-2* (pCMY-2), along with the *Salmonella* virulence plasmid (pSTV) were selected to evaluate the accessory genome. We found four multilocus genotypes, STs 19, 213, 302 and 429; ST19 was supported as the founder genotype. The most abundant genotypes, ST213 and ST19, were found in the four geographic regions and in almost all the sampled years. Interestingly, ST213 was more prevalent in food-animals than in humans, where ST 19 was predominant. We found a strong association between STs and antimicrobial resistance. ST213 strains presented higher percentages of resistance than ST19 strains, and all the strains resistant to ceftriaxone belonged to ST213. The resistance patterns varied across geographic locations. Yucatan was the state with the higher level of multidrug resistance, with an average of seven resistances per strain; while Sonora presented the lowest levels of resistance with an average of four. Furthermore, the ST213 ceftriaxone resistant strains displayed a differential geographic pattern, ranging from 100% of the ST213 strains in Yucatan to 0% in Sonora. We found strong associations among chromosomal genotypes and accessory genes. The general patterns of association can be summarized as follows: 1) the strains harbouring pSTV were ST19 or ST302; 2) all the strains with SGI1 were ST19 and most carried pSTV; 3) all the strains harbouring pCMY-2 were ST213; and 4) the abundant integron carrying *dfrA12*, *orfF* and *aadA2* was present only in ST213 strains. The mapping of accessory genes and multilocus genotypes on the dendrogram derived from macrorestriction fingerprints allowed the establishment of genetic compartments within the population. The associations among chromosomal genotypes and accessory genes, suggests that this Mexican *Salmonella* Typhimurium population has been derived recently and has a clonal genetic structure, with low levels of genetic exchange among genetic compartments. It is noteworthy that ST213 did not harbor the pSTV virulence plasmid yet it could cause infection in humans.

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4. MRSA Strikes Back!

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平松啓一

Since the introduction of penicillin G into practical use in 1940s, *Staphylococcus aureus* has always outwitted our repeated attempts to eradicate it. Now, *S. aureus* has become a symbol of our unattainable dream of anti-infective chemotherapy. Not only in the hospital but also in the community, methicillin-resistant *S. aureus* (MRSA), the historical stumbling block of our efforts, is still causing trouble after its first isolation in 1960, and showing no sign of decline in the future to come. Why is the organism so flexible and tenacious? Thanks to the development of high-throughput sequencing technologies, we have started to take a glimpse of the secret how the organism has conquered our "silver bullets" developed in the last century. It was a memorable experience for us to have uncovered the genomic structure of *S. aureus* in 2001, and have witnessed how skillfully and dramatically it could change its genetic traits in adverse environment. We now recognize that staphylococcal cassette chromosome (SCC), as an efficient interspecies transfer system of genetic information, has greatly contributed to the evolution of MRSA. Another secret of flexibility of *S. aureus* genome comes from its versatile regulatory system. Incorporation of point-mutations in the regulatory genes is responsible for the vancomycin resistance of vancomycin-intermediate *S. aureus* (VISA) strains. These'regulator mutations'seem to protect the cell by altering its physiology and preventing the access of the antibiotics to their targets of action. I shall explain recent advances in our genomic study on the evolutionary potential of *S. aureus*, which would give us an insight into our future strategy to treat this amazing organism.