Фонд оценочных средств

промежуточной аттестации

по дисциплине

Биомедицина на английском языке

Направление подготовки (специальность)
06.04.01 Биология

Направленность (профили)
Медико-биологические науки, Микробиология и вирусология, Генетика, Радиационная биология, Гистология

Присваиваемая квалификация
Магистр

Форма обучения
Очная

Год набора: 2025

Челябинск, 2025

1. ПАСПОРТ ФОНДА ОЦЕНОЧНЫХ СРЕДСТВ

Направление подготовки: 06.04.01 «Биология»

Направленность (профиль): «Медико-биологические науки, Микробиология и вирусология, Генетика, Радиационная биология, Гистология»

Дисциплина: «Биомедицина на английском языке»

Семестр изучения: 2

Форма промежуточной аттестации: зачёт

2. ПЕРЕЧЕНЬ ФОРМИРУЕМЫХ КОМПЕТЕНЦИЙ И ЭТАПЫ ИХ ФОРМИРОВАНИЯ

2.1. Компетенции, закреплённые за дисциплиной

Изучение дисциплины **«Биомедицина на английском языке»** направлено на формирование следующих компетенций:

Коды компетенции (по ФГОС)	Содержание компетенций согласно ФГОС	Содержание и коды индикаторов	Перечень планируемых результатов обучения по дисциплине
1	2		3
УК-4	Способен применять современные коммуникативные технологии, в том числе на иностранном(ых) языке(ах), для академического и профессионального взаимодействия и этическую ответственность за принятые решения	УК-4.1 Обладает знаниями особенностей и правил личной и профессиональной устной и письменной коммуникации, в том числе на иностранном(ых) языке(ах)	Знать: Для достижения УК-4.1 знать: правила составления деловых писем на английском языке Уметь: Для достижения УК-4.1 уметь: представить результаты своей научной работы на русском и английском языках; понимать тексты, аудио- и видеоматериалы на английском языке по теме профессиональной деятельности Владеть: Для достижения УК-4.1 владеть: навыками корректного перевода специальных научных текстов, посвящённых направлению профессиональной

			деятельности
ПК-1	Готовность к коммуникации в устной и письменной формах на государственном языке Российской Федерации и	ПК-1.2 Анализирует нормативные документы, регламентирующие организацию и методику проведения научно-исследовательских и производственно-технологических работ биологического профиля	Знать: Для достижения ПК-1.2 знать: особенности англоязычной научной-технической терминологии и понятийного аппарата в области профиля программы магистратуры Уметь: Для достижения ПК-1.2 уметь: выделять главные и наиболее существенные моменты в текстах англоязычных научных статей Владеть: Для достижения ПК-1.2 владеть: навыком постоянного критического мониторинга интернет-ресурсов на предмет новейших достижений в научно-практической области, соответствующей профилю программы магистратуры

3. СОДЕРЖАНИЕ ОЦЕНОЧНЫХ СРЕДСТВ ПО ДИСЦИПЛИНЕ

3.1 Виды оценочных средств

№ п/п	Код компетенции/планируемые результаты обучения	Контролируемые темы / разделы	Наименование оценочного средства для текущего контроля	Наименование оценочного средства для промежуточной аттестации / № задания
1.	Знать: Для достижения УК-4.1 знать: правила составления деловых писем на английском языке Уметь: Для достижения УК-4.1 уметь: представить результаты своей научной работы на русском и английском языках; понимать тексты, аудио- и видеоматериалы на английском языке по теме профессиональной деятельности Владеть: Для достижения УК-4.1 владеть: навыками корректного перевода специальных научных текстов, посвящённых направлению профессиональной деятельности	1. Научная и деловая коммуникация на английском языке. 2. Английская научная лексика различных биомедицинских профилей.	1. Письменное задание 2.Перевод научного текста	зачёт

2.	Знать: Для достижения УК-4.1 знать: правила составления деловых писем на английском языке Уметь: Для достижения УК-4.1 уметь: представить результаты своей научной работы на русском и английском языках; понимать тексты, аудио- и видеоматериалы на английском языке по теме профессиональной деятельности Владеть: Для достижения УК-4.1 владеть: навыками корректного перевода специальных научных текстов, посвящённых направлению профессиональной деятельности	1. Научная и деловая коммуникация на английском языке. 2. Английская научная лексика различных биомедицинских профилей.	1. Письменное задание 2. Аудирование 3. Перевод научного текста	зачёт

3.	Знать: Для достижения ПК-1.2 знать: особенности англоязычной научной-технической терминологии и понятийного аппарата в области профиля программы магистратуры Уметь: Для достижения ПК-1.2 уметь: выделять главные и наиболее существенные моменты в текстах англоязычных научных статей Владеть: Для достижения ПК-1.2 владеть: навыком постоянного критического мониторинга интернет-ресурсов на предмет новейших достижений в научно-практической области, соответствующей профилю программы магистратуры	1. Научная и деловая коммуникация на английском языке. 2. Английская научная лексика различных биомедицинских профилей.	1. Перевод научного текста 2. Краткое сообщение	зачёт

4.	Знать: Для достижения ПК-1.2 знать: особенности англоязычной научной-технической терминологии и понятийного аппарата в области профиля программы магистратуры Уметь: Для достижения ПК-1.2 уметь: выделять главные и наиболее существенные моменты в текстах англоязычных научных статей Владеть: Для достижения ПК-1.2 владеть: навыком постоянного критического мониторинга интернет-ресурсов на предмет новейших достижений в научно-практической области, соответствующей профилю программы магистратуры	1. Научная и деловая коммуникация на английском языке. 2. Английская научная лексика различных биомедицинских профилей.	1. Перевод научного текста 2. Краткое сообщение	зачёт

Примечание: Типовые задания, критерии и показатели оценивания в рамках текущего контроля представлены в рабочей программе дисциплины (модуля). Полные комплекты оценочных средств и контрольно-измерительных материалов хранятся на кафедре.

3.2 Содержание оценочных средств

Оценочные средства для текущего контроля представлены вопросами для письменного задания, текстами для перевода, текстами для аудирования, тематикой для краткого сообщения, оценочные средства для промежуточного контроля представлены итоговым заданием для зачёта.

3.2.1 Вопросы для письменного задания

1. What are you?
2. What is your special subject?
3. What field of knowledge are you doing research in?
4. Have you been working at the problem long?
5. Is your work of practical or theoretical importance?
6. Who do you collaborate with?
7. When do you consult your scientific adviser?
8. Have you completed the experimental part of your dissertation?
9. How many scientific papers have you published?
10. Do you take part in the work of scientific conferences?
11. Where and when are you going to get M.S. degree?

3.2.2 Тексты для перевода

3.2.2.1

A man dies because his body has rejected a heart transplant; a woman is crippled by rheumatoid arthritis; a child goes into a coma that is brought on by cerebral malaria; another child dies of an infection because of an immunodeficiency; an elderly man has advanced hepatic cirrhosis caused by iron overload. These five clinical situations are as diverse as can be, yet all have one thing in common: the cause of all of them involves the human leukocyte antigen (HLA) system, the human version of the major histocompatibility complex (MHC). Malfunction of the HLA system, which is at the root of these and many other clinical disorders, has such wide- ranging effects not only because of the system‘s role in the adaptive immune response, but also because of its genetic complexity. The HLA complex on chromosome 6 contains over 200 genes, more than 40 of which encode leukocyte antigens. The rest are an assortment of genes that are not evolutionarily related to the HLA genes themselves, although some are involved with them functionally. Many genes within this complex have nothing to do with immunity. The HLA genes that are involved in the immune response fall into two classes, I and II, which are structurally and functionally different. The class I genes code for the a polypeptide chain of the class I molecule; the b chain of the class I molecule is encoded by a gene on chromosome 15, the beta 2 -microglobulin gene.The a chain has five domains: two peptide-bindingdomains (a 1 and a 2), one immunoglobulin-like do-main (a 3), the transmembrane region, and the cytoplasmic tail. There are some 20 class I genes in the HLA region;three of these, HLA-A, B, and C, the so-called classic, or class Ia genes, are the main actors in the immunologic theater.The class II genes code for the a and b polypeptide chains of the class II molecules. The designation of their loci on chromosome 6 consists of three letters: the first (D) indicates the class, the second (M, O, P, Q, or R) the family, and the third (A or B) the chain (a or b, respectively). HLA-DRB, for example, stands for class II genes of the R family coding for the b chains. The individual genes of the HLA system are differentiated by Arabic

numbers, and the notation for the numerous allelic variants of these genes is a number preceded by an asterisk. For example, HLA-DRB1*0401 stands for allelic variant 0401 of gene 1, which encodes the b chain of a class II molecule belonging to the R family. Each of the class II a and b chains has four domains: the peptide-binding domain (a 1 or b 1), the immunoglobulin-like domain (a 2 or b 2), the transmembrane region, and the cytoplasmic tail. Class I genes are expressed by most somatic cells, although the level of expression varies depending on the tissue. By contrast, class II genes are normally expressed by a subgroup of immune cells that includes B cells, activated T cells, macrophages, dendritic cells, and thymic epithelial cells. In the presence of interferon-g, however, other types of cells can express class II HLA molecules. The function of both class I and class II molecules is the presentation of short, pathogen-derived peptides to T cells, a process that initiates the adaptive immune response. To understand this function, it is necessary to place it in the context of the cell‘s physiology, in particular the process of waste disposal. ANTIGEN PROCESSING AND PRESENTATION. Cells are equipped with an enviably clean and efficient system of waste disposal and recycling. Aspecial molecule, ubiquitin, marks worn-out proteins for dumping. These proteins unfold with the help of other specialized molecules, the chaperones, and the polypeptide chains arethen fed into barrel-shaped structures, the proteasomes, which chop them up into short fragments. The peptides emerging from the proteasome are either degraded into amino acids in the cytosol or transferred into the endoplasmic reticulum. Extracellular proteins take a different route to degradation. They are herded into small bags that invaginate from the plasma membrane into the cytoplasm. The bags are then pinched off as endocytic vesicles, and they fuse with primary lysosomes, which are loaded with an assortment of proteolytic enzymes, to form endosomes. Within the endosomes, the ingested proteins are degraded, first to peptides and then, in some vesicles, into amino acids for reuse. This mode of protein processing must have evolved at an early stage in the history of living forms. Later, the jawed vertebrates found a new use for it by enlisting it in the defense of the body against pathogens. Normally, the proteins that undergo recycling are the organism‘s own, but in infected cells, proteins originating from the pathogen are also routed into the processing pathways. With the exception of jawed vertebrates, no organisms appear to make a distinction between peptides derived from their own (self) proteins and those derived from foreign (nonself) proteins. Jawed vertebrates, by contrast, use the peptides derivedfrom foreign (usually microbial) proteins to mark infected cells for destruction. In an uninfected cell,
—house kee pi ng‖ proteasomes c ontinuously c hurn out se lf pe ptides, som e of whic h are pic ked up by m olec ule s called —tra nsporte rs associa te d with a ntige n processing,‖ or TAPs, enc oded by the TAP1 a nd TAP2 ge nes. The TAP1 and TAP2 proteins interact to form a channel for transporting peptides across the membrane of the endoplasmic reticulum. Peptides released by proteasomes bind to the cytosolic surface of the TAP molecule and are ferried through this channel. On the luminal surface of the endoplasmic reticulum, queuing up like trucks waiting to be loaded with cargo, are the class I molecules. The two polypeptide chains of the class I molecules, thea chain and the beta 2 -microglobulin, are manufactured separately on ribosomes attached to the cytosolic surface of the endoplasmic reticulum, but as they come off the assembly line, they thread through special channels to make their way to the luminal surface of the endoplasmic reticulum. There, the emerging chains are attended by asuite of molecular chaperones — calnexin, calreticulin, endoplasmic reticulum p57, TAP-binding protein (also referred to as tapasin), and perhaps others— which ensure that the polypeptides do not fold prematurely, that they are properly glycosylated, that the a chain meets beta 2-microglobulin at the appropriate time, and that when this moment comes, the union proceeds without a hitch. A class I moleculeis then pinioned by the TAP-binding proteinto the TAP molecule for loading. When a suitable peptide emerges from the TAP channel, the peptide-binding groove of the waiting class I molecule snags it. The loaded molecule then undocks from the complex of TAP- binding protein and TAP and sets off on a journey to the surface of the cell. There, the class I molecule remains anchored in the plasma membrane by the transmembrane region of the a chain. In this position, it displays the bulkof the a chain (the a 1, a 2, and a 3 domains), the peptide, and the associated beta 2 -microglobulin to other cells. In the meantime, the class II molecules are also preparing to receive peptides generated by the endocytic protein- processing pathway. Like the two chains of class I molecules, those of class II molecules are manufactured separately on the cytosolic surface of the endoplasmic reticulum and then brought together, folded, and assembled on the luminal surface of the structure with the assistance of chaperones. Unlike class I molecules, however, class II molecules are not loaded with peptides in the endoplasmic reticulum. Instead, they associate with a protein produced in the endoplasmic reticulum, the invariant chain, part of which acts as a stopper for the peptide-binding groove and thereby precludes premature loading of peptides. Enclosed in membranous vesicles, the complexes of class II molecules and invariant chains journey to the region of the cytoplasm in which they intersect with endosomes with their cargo of exogenous proteins. The transporting vesicles and the endosomes fuse to form the MHC class II compartment, in which proteases degrade the exogenous proteins and the bulk of the invariant chain(the class II molecules being remarkably resistant to the action of these enzymes). This process leaves behind the piece of the invariant chain that functions as a stopper in the peptide-binding groove. Ultimately, however, the stopper is also dislodged by class II molecules specialized in this task (HLA-DM), and a peptide derived from an

exogenous protein slips into the groove. The peptide-laden class II molecules are then exported to the surface of the cell. Protein processing and loading of peptides onto class I molecules are taking place all the time in most cells. There is always plenty of material to feed the processing machinery, because worn-out, damaged, and misfolded proteins are continuously being de-graded and replaced by new ones. In addition to processing by proteasomes, some proteins are also degraded into peptides by soluble enzymes in the cytosol. By contrast, the processing of exogenous proteins and the loading of peptides onto class II molecules are normally restricted to B cells, macrophages, and dendritic cells, which are very efficient in taking up material by endocytosis or phagocytosis. Although most class I and class II molecules form complexes with peptides derived from endogenous and exogenous proteins, respectively, this demarcation is by no means absolute. Class I molecules containing peptides derived from exogenous (e.g., bacterial) proteins and class II molecules laden with peptides generated from endogenously synthesized (e.g., viral) proteins exist, but how these complexes arise is not entirely clear. The consequence of protein processing is that the surfaces of cells become adorned with peptide-laden HLA molecules, amounting on a per cell basis to roughly 100,000 to 300,000 class I or class II products of each of the highly expressed HLA loci. Since each HLA molecule has one peptide bound to it, each uninfected cell displays hundreds of thousands of self peptides on its surface. Some of these peptides are present in the thousands, whereasothers are represented by a few copies; most peptide species have100 or so copies on the surface of each cell. Each cell thus displays a heterogeneous collection of peptides, and the surface of a cell resembles rows of well- stocked stalls at a bazaar, with bargain hunters scrutinizing the wares. But if, in this metaphor, the vendors are the HLA molecules and the peptides the goods,who are the potential buyers? They are a group of lymphocytes reared in the thymus and then turned loose to roamthe body — the T cells.

3.2.2.2

The link between the microbes in the human gut and the development of obesity, cardiovascular disease and metabolic syndromes, such as type 2 diabetes, is becoming clearer. However, because of the complexity of the microbial community, the functional connections are less well understood. Studies in both mice and humans are helping to show what effect the gut microbiota has on host metabolism by improving energy yield from food and modulating dietary or the host-derived compounds that alter host metabolic pathways. Through increased knowledge of the mechanisms involved in the inter-actions between the microbiota and its host, we will be in a better position to develop treatments for metabolic disease.

Changes to lifestyle and an increase in the availability of energy-rich foods are important contributors to the world-wide obesity epidemic. The microbial inhabitants of the gut can also have an influence on metabolic processes, such as energy extraction from food, and should be considered an environmental factor that contributes to obesity and its comorbidities (such as insulin resistance, diabetes and cardiovascular disease). Culture- independent methods to study microbial communities have advanced our knowledge of this human gut microbiota. Profiling of the common proxy for this community, the faecal microbiota, by 16S ribosomal RNA surveys and by direct sequencing of genetic material have shown that the human gut microbiota is a complex community of 100 trillion archaeal and bacterial cells distributed over more than 1,000 species. The community is dominated by bacteria, with more than 90% of the species belonging to Firmicutes and Bacteroidetes. Each personhas a distinct and highly variable microbiota, but a conserved set of gut colonizers (the core gut microbiota) and genes (the core microbiome) are shared among individuals and may be required for the correct functioning of the gut. Germ-free mice are those born and reared without exposure to any live microbes, and they provide a powerfultool for understanding the effects of the gut microbiota on host physiology. These mice can be colonized either with selected microbial species or whole communities from mice or humans to examine the transmissibility of physiological and pathological phenotypes, and to test what role the microbiota has in a particular phenotype. The gut microbiota in these mice modulates bone-mass density and promotes fat storage, intestinal angiogenesis and the development of an immune response. In this Review, we discuss the metagenomic and gnotobiotic-based evidence for the role of the gut microbiota in energy metabolismand the possible links with obesity.

Obesity. Gut microbiota composition is altered in people who are obese, and it can respond to changes in body weight. Genetically obese ob/ob mice are hyperphagic as a result of a mutation in the gene that encodes the satiety-promoting hormone leptin. The caecal microbiota of these mice contains more Firmicutes and fewer Bacteroidetes than that of their lean wild-type littermates, even when the mice are fed the same low-fat, polysaccharide-rich diet. Similar changes have also been seen in the faecal microbiota of humans who are obese. Bacteroidetes levels increase when weight is reduced, either by fat- or carbohydrate-restricted diets, suggesting that Bacteroidetes may be responsive to calorie intake. A similar effect has also been observed in people who lost weight after a Roux-en-Y gastric bypass procedure. In these patients, increased levels of Bacteroides and Prevotella were negatively correlated with energy intake and adiposity. Other studies showed no such shift in the Firmicutes–Bacteroidetes ratio, but this may be because they used different clinical criteria (such as level of obesity, age, degree of weight loss and duration of calorie restriction), geographical locations, population sizes and

microbiota-profiling methodologies. Although obesity and energy intake can affect the microbial composition, whether the gut microbiota contributes to obesity in humans is unclear. A gastric bypass promotes sustained weight reduction and diminishes the risk of diabetes and cardiovascular disease for people who are obese. This knowledge has allowed the relationship between microbiota and obesity to be explored further. After a gastric bypass, diabetes can resolve before patients begin to lose weight, suggesting that this type of surgery has a direct antidiabetic effect. Exactly how this happens is not clear, but a shift in the composition of the faecal microbiota of humans suggests the gut microbiota contributes to the improved metabolic phenotype after a gastric bypass. The beneficial microbe Faecalibacterium prausnitzii, in particular, is less abundant in patients who are obese and diabetic, but increases after surgery. Levels of F. prausnitzii are negatively correlated with inflammatory markers, indicating that the bacterium may modulate systemic inflammation (common to diabetes and obesity) and contribute to the amelioration of diabetes. In addition, germ-free mice do not develop diet-induced obesity, and treatment of obese mice with antibiotics reduces adiposity and adipose inflammation, and improves glucose metabolism, further supporting the benefits of inducing a shift in microbiota composition.

Energy harvest. Carbohydrates are important sources of energy for human and microbial cells. Human enzymes cannot degrade most complex carbohydrates and plant polysaccharides. Instead, the non-digestible carbohydrates, including cellulose, xylans, resistant starch and inulin, are fermented in the colon by its microbiota to yield energy for microbial growth and end products such as short-chain fatty acids (SCFAs), mainly acetate, propionate and butyrate, which have profound effects on gut health as, for example, an energy source, an inflammation modulator, a vasodilator and part of gut motility and wound healing. In addition, SCFAs are energy substrates for the colonic epithelium (butyrate) and peripheral tissues (acetate and propionate). The patterns of intestinal fermentation, and consequently the types and amount of SCFAs produced, are determined by how much carbohydrate is consumed and the composition of the gut microbiota. For example, fermentation of dietary fructans increases when gnotobiotic mice that have been colonized with Bacteroides thetaiotaomicron, are co- colonized with Methanobrevibacter smithii. B. thetaiotaomicron produces more acetate and formate, and M. smithii uses formate for methanogenesis. The interactions promote more efficient carbohydrate fermentation and increased energy absorption from the gut, resulting in increased adiposity in the co-colonized mice compared with mice colonized with only B. thetaiotaomicron. The composition of the gut microbiota and the metabolic interactions between its species may therefore affect food digestion and energy harvest. Direct evidence for the role of the microbiota in energy harvest and fat deposition comes from germ-free rats, which have reduced intestinal levels of SCFAs, and twice as much urinary and faecal excretion of calories as that of conventional rats fed the same polysaccharide-rich diet. The germ-free rodents compensate for the reduced energy harvest by increasing their food intake. Germ-free mice also have reduced adiposity compared with their conventional counterparts, but adiposity is normalized when they are colonized with a healthy microbiota for 14 days. Microbial energy harvest in obesity has been investigated in conventional genetically obese ob/ob mice, which have increased amounts of SCFAs in their caecum and reduced energy content in their faeces compared with their lean littermates. Metagenomic sequencing of the caecal microbiota showed an enrichment of gene functions that were related to the degradation of dietary polysaccharides in the microbiome of ob/ob mice. This finding was also true of humans: the faecal microbiota of people who are obese has an increased capacity to harvest energy. In mice, the obese phenotype was transmissible through microbiota transplants, and germ-free mice colonized with the microbiota from obese donors gained twice as much fat as those colonized with the microbiota from lean donors.The role of the gut microbiota in promoting energy harvest from diet and fat deposition has been clearly demonstrated in mice, but most of the evidence in humans has come from indirect studies. For instance, people who are obese have higher levels of ethanol in their breath than lean people, indicating altered fermentation and a greater number of faecal SCFAs, which may suggest increased microbial energy harvest.

Diet alters the gut microbiota Diet is known to modulate the composition of the gut microbiota in humans and mice. Long-term dietary habits have a considerable effect on the human gut microbiota. For example, children in a rural African village, who consumed high amounts of plant polysaccharides, had low levels of Firmicutes and increased levelsof Bacteroidetes — mainly Prevotella and Xylanibacter — in their faecal microbiota compared with Italian children, who had high levels of Enterobacteriaceae — mainly Shigella and Escherichia. Prevotella and Xylanibacter are known to degrade cellulose and xylans, and are associated with increased faecal SCFAs,suggesting that the gut microbiota of the children living in rural Africa had adapted to maximize energy extractionfrom a diet rich in fibre. Human gut microbiota can be divided into three discrete compositions. However, this concept is currently being challenged as enterotypes maybe more of a gradient than discrete entities. Each enterotype is dominated by a different genus — Bacteroides, Prevotella or Ruminococcus — but not affected by gender, age or nationality. Enterotypes dominated by Bacteroides or Prevotella are associated with the consumption of a diet rich in protein and animal fat, or carbohydrates, respectively. The Ruminococcus enterotypeis not well separated and is partly merged with the Bacteroides enterotype. This division supports the association between Prevotella and a diet high in carbohydrates, which was seen in children from rural Africa. A 10-day

dietary intervention, hsuggesting that a long-term change may be required to provoke a major shift in gut microbiota composition. Changes in daily carbohydrate intake may affect specific groups of colonic bacteria overa short period of time. Consum ption of the pre biotic inulin increases the leve ls of F. pra usnitz ii a nd Bifidobac terium sp. in huma ns. Similarly, prebiotics promote a selective increase in Bifidobacterium sp. in diet- induced obese mice, and this increase is correlated with reduced adiposity and levels of microbe-derived inflammatory molecules, such as lipopolysaccharide, compared with mice that are fed a high-fat diet without prebiotics. Human diets that are supplemented with resistant starch have increased faecal levels of Ruminococcus bromii and Eubacterium rectale, which correlates with fibre fermentation. Consumption of resistant starch also improves insulin sensitivity, but the variation in the microbial response to changes in resistant starch between individuals suggests successful dietary interventions need to be personalized.The gut microbiota also reacts to dietary fat. Mice fed on high-fat diets have reduced numbers of Bacteroidetes, and increased numbers of Firmicutes and Proteobacteria. This change is rapid, occurring within 24 hours. Transplantation of the caecal microbiota from obese mice fed on high-fat diets into germ-free recipients increases adiposity significantly more than transplantation of a lean microbiota. The altered microbial community of obese mice seems to have some role in promoting diet-induced obesity, but the mechanisms that cause this are unknown. A change in diet clearly alters the gut microbiota, and these alterations may contribute to the host‘s metabolic phenotype. Further metatranscriptomic and proteomic studies should provide insight into the response of microbial function as a result of a dietary shift.

Regulation of permeability and inflammation. Obesity, insulin resistance and development of type 2 diabetes are associated with systemic and adipose tissue inflammation. The gut microbiota is a rich source of molecules such as lipopolysaccharide and peptidoglycan that may cause inflammation in peripheral tissues of the body. Colonization of germ-free mice with Escherichia coli is sufficient to augment macrophage infiltration of adipose tissue and polarize macrophages towards the expression of pro-inflammatory cytokines. Plasmalipopolysaccharide levels increase in patients with type 2 diabetes, and feeding lipopolysaccharide to mice for 4 weeks increase adipose tissue inflammation and reduce insulin sensitivity. These findings suggest that the gut microbiota may affect host metabolism by altering adipose tissue inflammation. Higher numbers of T cells and mast cells, and lower numbers of regulatory T cells are also involved, but if and how the gut microbiota affects these cells and whether such interactions contribute to metabolic abnormalities is unclear. Plasma lipopolysaccharide levels seem to rise with higher fat intake in mice and humans. Two hypotheses have been madeto explain the mechanism: lipopolysaccharide is taken up with dietary fats in chylomicrons, or lipopolysaccharide reaches the circulation because the gut is more permeable in obese mice. A connection between metabolism and the function of the epithelial barrier is thought to exist. Targeted deletion of fatty acid synthase — encoded by the Fas gene — in the gut epithelium of mice showed that epithelial de novo lipogenesis is required to maintain barrier function. Fas-deficient epithelium has increased permeability and, as a result, increased colonic levels of proinflammatory cytokines and high serum lipopolysaccharide. These phenotypes were corrected by antibiotic treatment, suggesting a reciprocal interaction between microbiota, altered epithelial permeability and host metabolism. A similar connection between gut permeability and type 2 diabetes in humans could also be present. Permeability is correlated with increased visceral adiposity and hepatic steatosis, and those with high visceral adiposity and type 2 diabetes have increased levels of bacterial DNA in their blood. However, inflammation may increase permeability in the gut, and further investigation into whe ther increase d pe rmea bility ca uses a dipose inflam mation or inc rease d inflam mation c ontributes to inc rease d permeability is needed. Either way, the gut microbiota modulates permeability that may contribute to adipose inflammation and cause insulin resistance. Lipopolysaccharide molecules bind to Toll-like receptor 4 (TLR4), and peptidoglycan to nucleotide-binding oligomerization domain (NOD) receptors, both of which activates proinflammatory signalling cascades. Deletion of TLR4 in haematopoietic cells by generating bone-marrow chimaeras shows that TLR4 activation in macrophages of mice fed a high-fat diet is required for the development of fasting hyperinsulinaemia, and insulin resistance in liver and adipose tissue but not for the development of obesity. The innate immune system, however, also modulates microbial composition, which may have autonomous effects on host metabolism. Mice deficient inTLR5 have an altered microbial ecology and exhibit metabolic - syndrome signs, such as obesity, insulin resistance and dyslipidaemia, which are, in part, associated with increased food consumption. Transplantation of the gut microbiota from Tlr5 -deficient and wild-type mice into germ-free recipients shows that the phenotypes are transmissible, and suggests that the gut microbiota alone can mediate disease. Microbe-associated molecular patterns, including lipopolysaccharide and peptidoglycan, can be recognized by nucleotide-binding domain and leucine-rich-repeat-containing proteins (NLRPs), which form the inflammasome complex together with the apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC). Obesity is associated with increased adipose expression of NLRP3 in mice and ablation of NLRP3 enhances insulin signalling. However, inflammasomes may be linked to gut microbiota and host metabolism. NLRP3, NLRP6 and ASC are important regulators of microbial ecology in mice, and deletion of their genes increases the number of

Bacteroidetes (Prevotellaceae) and TM7. In particular, deficiency in Nlrp6 results in altered gut microbial ecology that predisposes mice to colitis, and inflammasome complexes that do not contain NLRP3 or NLRP6 are associated with an altered gut microbiota and promote NAFLD and non-alcoholic steatohepatitis (NASH). Importantly, wild-type mice housed with disease-prone Asc−/− mice develop NAFLD or NASH, providing direct evidence that an altered gut microbiota may cause these diseases. Alterations to gut microbiota composition are associated with an increased influx of TLR4 and TLR9 ligands — presumably lipopolysaccharide and bacterial DNA — respectively, to the liver through the portal vein. Mice deficient in TLR signalling in the liver are therefore protected from developing conditions related to metabolic syndrome such as obesity, NAFLD and NASH. The interaction between diet, host and gut microbiota may modulate gut permeability that leads to an influx of proinflammatory molecules and subse que nt activation of infla mmatory signalling pathwa ys in periphera ltissues tha t ma y ca use obesity, stea tosis and insulin resistance.

Future research. The gut microbiota is increasingly being accepted as an environmental factor that affects host metabolism and contributes to associated pathological conditions, such as obesity, diabetes and cardiovascular disease. However, the contribution that the gut microbiota makes to causing obesity and diabetes in humans is unclear. This is probably because the heterogeneous aetiology of obesity and diabetes can be associated with different microbes; studies are underpowered and include participants with diverse ethnic origin and food habits; the composition of the gut microbiota has large interpersonal variation; and different methods, with specificbiases, have been used to profile the microbiota. Cheaper sequencing and improved bioinformatics tools for the analysis of the gut microbiota will allow more researchers to use metagenomic sequencing and avoid primer and polymerase chain reaction biases linked to 16S rRNA gene surveys. Although useful, metagenomic approaches should be complemented by metatranscriptomics and metaproteomics to assess which microbial genes and proteins are expressed in specific conditions. One of the main challenges is to obtain robust predictive biomarkers for obesity and diabetes on the basis of the gut microbiota, for which improved study designs and analytical methods are essential. Much of the focus has been on the faecal microbiota, but many metabolic functions also occur in the small intestine. Sampling intestinal specimens might contribute to the identification of microbial biomarkers for health and disease, and although challenging, more emphasis should be placed on examining its microbiota and the effects on host metabolism. Studies in humans tend to be correlative, so the role of the microbiota in obesity and its comorbidities in humans remains to be proven. However, this role can be examinedin animal studies. Germ-free mice can be _humanized‘ by colonizing them with human intestinal communities, providing tools for examining the function of a specific human microbiota and testing how it interacts with specific diets. Genetically engineered germ-free mice could help to identify the molecular mechanisms by which the gut microbiota affects host metabolism. Pigs have similar gastrointestinal tracts and diets to humans, so they could be useful animal models in which to test dietary interventions and to manipulate the gut microbiota to improve health and prevent disease. Accumulating evidence indicates that the gut microbiota may be a target for treating metabolic diseases. Supplementing the diet with non-digestible food ingredients, or prebiotics, that stimulate the expansion of specific microbes to improve metabolic regulation can be a therapy. Probiotics may be an interesting approach for prevention of obesity and related diseases. But to determine the effects of both of thesetherapies, double-blind, placebo- controlled studies are required. Therapies that replace unhealthy with a healthy microbiota through transplantation have been used successfully since 1958 for the treatment of antibiotic-related diarrhoeal colitis. Recently, transplantation of healthy lean microbiota improved insulin signalling in participants with metabolic syndrome. Although a promising technique, transmission of unknown and potentially pathogenic bacteria and viruses from an unfractionated gut microbiota may have risks for the recipient. Using microbiota- based interventions to treat obesity will require probiotics that are selected for specific clinical manifestations of metabolic syndrome.

3.2.2.3

Abstract: Staphylococcus aureus is a common and often virulent pathogen in humans. This bacterium is widespread, being present on the skin and in the nose of healthy people. Staphylococcus aureus can cause infections with severe outcomes ranging from pustules to sepsis and death. The introduction of antibiotics led to a general belief that the problem of bacterial infections would be solved. Nonetheless, pathogens including staphylococci have evolved mechanisms of drug resistance. Among current attempts to address this problem, phage therapy offers a promising alternative to combat staphylococcal infections. Here, we present an overview of current knowledge on staphylococcal infections and bacteriophages able to kill Staphylococcus, including experimental studies and available data on their clinical use. Keywords: bacteriophages; Staphylococcus aureus; MRSA

Introduction. Infections by bacteria have been one of the major causes of health disorders throughout human history. After the development of antibiotics, a general belief arose that the problem of bacterial infections would

be solved. Nonetheless, pathogens have evolved sophisticated mechanisms of drug resistance. Due to their high capacity to acquire resistance to antibiotics, there are not enough chemotherapeutics to destroy bacteria and to counteract the problem of infections in the human population. As a result, antimicrobial resistance has emerged as one of the most serious health threats, prompting widespread efforts to develop new antibacterials. Unfortunately, drug-resistant bacteria are responsible for a significant number of deaths worldwide every year. This has been pointed out in reports of the European Medicines Agency and by the U.S. Centers for Disease Control and Prevention (CDC) in the United States. Currently there is a call for investigations of new means of treatment, e.g., therapeutic applications of bacteriophages. Due to the major contribution of multi-drug resistant Staphylococcus aureus to the re-emerging problem of bacterial infections, we propose an overviewof staphylococcal bacteriophages and their future potential for the medicine.

Staphylococcal Phages in Medicine. Staphylococcal phages represent the most popular group among therapeutic phage strains characterized by good efficacyinthe treatment of bacterial infections. Specifically, phages able to kill S. aureus have been widely studied in the treatment of various human diseases, e.g., venous leg ulcers and eye infections, septicemia, staphylococcal lung infections, and others. In the early 20th century, very promising effects of phage treatment of infections caused by Staphylococcus were relatively often described. Good efficacy in the treatment was demonstrated by specific phages or phage cocktails. Even severe cases of bacteremia and sepsis were reported as treatable with a phage. The first report onmedical use of staphylococcal phages dates back to 1921 when R. Bruynoghe and J. Maisin treated skin infection caused by S. aureus. The phages were injected around surgically opened lesions. Regression of infection was observed within 24–48 hours. Good efficacy was a noticeable feature of this group of phages from the beginning and early stages of phage therapy. In 1936, Sauve et al. used phages in septicemia caused by Staphylococcus. Within 3–5 hours after phage administration a marked decrease of patients‘ body temperature was observed. These authors reported that a severe case of septicemia had been cured within 24 hours of intravenous bacteriophage infusion. They postulated that phage therapy should always be preceded by surgical treatment including incision and drainage, if necrotic tissue is present. Goodresults of treatment with lytic phage cocktails were reported by MacNeal and Frisbee in staphylococcal bacteremia. In the 1970s, Sakandelidze et al. conducted studies in Tbilisi (Georgia) using phages against Staphylococcus, Streptococcus and Proteus or a mixture of phages called ―diphage (Staphylococcus and Proteus phages). Patients suffering from antibiotic-resistant osteomyelitis, peritonitis, post-surgical wound infections and lung abscess were treated with phages. The authors applied phages subcutaneously or via a surgical drain daily for 5–10 days, leading to an improvement in 92% of investigated cases. At the same time, Vieu compared phages isolated and prepared by the Bacteriophage Service at the Pasteur Institute during 1969–1974, including those targeting Staphylococcus mostly resistant to antibiotics. These studies concerned septicemia with endocarditis, chronic osteomyelitis, suppurative thrombophlebitis, pulmonary, and sinus infections, pyelonephritis, skin infections and furunculosis, which had not been repressed by extensive antibiotic treatment. This work resulted in the development of a set of commercially available (since 1976) therapeutic phage strains including more than 10 against Staphylococcus. Meladze et al., in 1982, compared phages to antibiotics in regard to their activity against S. aureus. Phages active against S. aureus were used to treat patients suffering from purulent disease of the lungs and pleura. The patients were divided into two groups. One of the groups was treated with phages intravenously, while the second received antibiotics. No side effects were observed in any of the patients, including those to whom the phages were administered intravenously. Full recovery was observed in 82% of the patients treated withphages, whereas only 64% of the patients in the antibiotic-treated group recovered completely. Even if not established or common, phage therapy trials have been carried out in Europe for several decades. In the 1980s, Ślopek et al. reported studies in patients with staphylococcal infections and patients with mixed infections including Staphylococcus. As a result of phage therapy they observed improvement in 75% of infected ulcerated varicose vein cases and in 100% of cases of gastrointestinal infections, pericarditis, and furunculosis, caused by Staphylococcus. Interestingly, the authors suggested that phage-monotherapy is more effective than parallel administration of phages and antibiotics. In recent studies in the Institute of Immunology and Experimental Therapy (IIET) reported by Międzybrodzki et al. anti-staphylococcal phages were used in respiratory and urinary tract, orthopedic and skin infections. Positive results (health improvement or bacterial eradication) were observed in 36.7% of patients. Studies of the same group also involved orthopedic infections, in which phages were administered orally, topically, or both orally and topically. Comparison of staphylococcal phages to Pseudomonas phages revealed that staphylococcal phages were more effective when applied topically (47.1% of good response in staphylococcal phage treatment in comparison to 33.3% in other phages treatment). The topical application of phage preparations was the most effective in general and resulted in improvement in 34.6% of cases. Pathogen eradication and/or recovery was observed in 15.4% of cases. In patients with respiratory tract infections a good response was observed in 25% of cases, while in 16.7% of patients pathogen eradication and/or complete recoverywas achieved. Patients with skin infections were treated with phages by the topical route, which resulted in a goodresponse in 16.7% of patients. Data on staphylococcal phage penetration in humans are scarce, but Weber et al.

reported studies of penetration of orally administered staphylococcal phages in serum or in the urinary tract. In those studies patients with suppurative infections caused by Staphylococcus were treated with phages. After 10 days of therapy, phages were found in 84% of serum samples and in 35% of urine samples, indicating a high bioavailability of the phage. In studies by Kucharewicz-Krukowska et al. a 37.5% increase in the level of anti- staphylococcal phage antibodies was observed in patients subjected to phage therapy. This increase had no impact on the efficacy of the phage therapy. Summarizing data reported by IIET, staphylococcal phages administered by different routes—topically, orally, or both—are effective in the treatment of bacterial infections, which correlates with their good penetration in the system. Phages used in therapy can bring complete eradication of bacteria, but ithas also been postulated that complete eradication might be unnecessary to achieve a significant improvement in the patient‘s health. Phage therapy in cancer patients with bacterial infections has been presented by the Russian scientists Kochetkova et al.. These authors reported a 74.7% positive result rate in patients treated with staphylococcal phages while general effectiveness of all tested phages was 81.5%. High efficiency of phage therapy in cancer patients was also observed in studies by Weber-Dąbrowska et al.. Negative results of anti- Staphylococcus aureus treatment have also been reported, e.g., in studies of therapeutic phage applications by Eaton and Bayne-Jones. In general, their report in JAMA had a dramatically negative impact on phage perception by medical and scientific communities. This discouraging publication provided consistent and convincing data only for the treatment of localized staphylococcal infections and cystitis. Most of the reports presenting clinicaluse of anti-S. aureus strain phages in humans imply that staphylococcal phages have good antibacterial properties in general. This is in line with the recent summaries of general phage therapy data presented by Abedon and Kutter. Anti-staphylococcal phages often show better results in comparison to other phage groups. No adverse effects of anti-staphylococcal phage therapy have been reported. Evaluation of enterotoxin content in staphylococcal lysates used in therapy revealed negative results, i.e., the enterotoxin level is below the detectable level. Different ways of phage application give positive results in the treatment of bacterial infections. There is a significant group of health disorders caused by Staphylococcus in which phage therapy has been shown to be effective.

3.2.2.4

Recent research has shown that inflammation plays a key role in coronary artery disease (CAD) and other manifestations of atherosclerosis. Immune cells dominate early atherosclerotic lesions, their effector molecules accelerate progression of the lesions, and activation of inflammation can elicit acute coronary syndromes. This review highlights the role of inflammation in the pathogenesis of atherosclerotic CAD. It will recount the evidence that atherosclerosis, the main cause of CAD, is an inflammatory disease in which immune mechanisms interact with metabolic risk factors to initiate, propagate, and activate lesions in the arterial tree. A decade ago, the treatment of hypercholesterolemia and hypertension was expected to eliminate CAD by the end of the 20th century. Lately, however, that optimistic prediction has needed revision. Cardiovascular diseases are expected to be the main cause of death globally within the next 15 years owing to a rapidly increasing prevalence in developing countries and eastern Europe and the rising incidence of obesity and diabetes in the Western world. Cardiovascular diseases cause 38 percent of all deaths in North America and are the most common cause of death in European men under 65 years of age and the second most common cause in women. These facts force us to revisit cardiovascular disease and consider new strategies for prediction, prevention, and treatment. Atherosclerotic lesions (atheromata) are asymmetric focal thickenings of the innermost layer of the artery, the intima. They consist of cells, connective-tissue elements, lipids, and debris. Blood-borne inflammatory and immune cells constitute an important part of an atheroma, the remainder being vascular endothelial and smooth- muscle cells. The atheroma is preceded by a fatty streak, an accumulation of lipid-laden cells beneath the endothelium. Most of these cells in the fatty streak are macrophages, together with some T cells. Fatty streaks are prevalent in young people, never cause symptoms, and may progress to atheromata or eventually disappear. In the center of an atheroma, foam cells and extracellular lipid droplets form a core region, which is surrounded by a cap of smooth-muscle cells and a collagen-rich matrix.Tcells, macrophages, and mast cells infiltrate the lesion and areparticularly abundant in the shoulder region where the atheroma grows. Many of the immune cells exhibit signs of activation and produce inflammatory cytokines. Myocardial infarction occurs when the atheromatous process prevents blood flow through the coronary artery. It was previously thought that progressive luminal narrowing from continued growth of smooth-muscle cells in the plaque was the main cause of infarction. Angiographic studies have, however, identified culprit lesions that do not cause marked stenosis, and it is now evident that the activation of plaque rather than stenosis precipitates ischemia and infarction. Coronary spasm may be involved to some extent, but most cases of infarction are due to the formation of an occluding thrombus on the surface of the plaque. There are two major causes of coronary thrombosis: plaque rupture and endothelial erosion. Plaque rupture, which is detectable in 60 to 70 percent of cases, is dangerous because it exposes prothrombotic material

from the core of the plaque —phospholipids, tissue factor, and platelet-adhesive matrix molecules — to the blood. Ruptures preferentially occur where the fibrous cap is thin and partly destroyed. At these sites, activated immune cells are abundant. They produce numerous inflammatory molecules and proteolytic enzymes that can weaken the cap and activate cells in the core, transforming the stable plaque into a vulnerable, unstable structure that can rupture, induce a thrombus, and elicit an acute coronary syndrome.To understand how this can happen, we need toidentify the key steps leading froma normal artery wall to a rupture-prone atherosclerotic plaque.

Gene-targeted mouse models. Clinical investigations, population studies, and cell-culture experiments have provided important clues to the pathogenesis of atherosclerosis. However,experiments in animals are needed to dissect the pathogenetic steps and determine causality. Atherosclerosis does not develop in laboratory mice under normal conditions. However, targeted deletion of the gene for apolipoprotein E (apoE-knockout mice) leads to severe hypercholesterolemia and spontaneous atherosclerosis. Atherosclerosis also develops in mice lacking low- density lipoprotein (LDL) receptors, especially when the mice are fed a fatty diet. One can use these knockout mice to study the relationship between hypercholesterolemia and atherosclerosis and to assess the effects of other genes and gene products on these conditions. By mating these mice with knockout mice lacking immunoregulatory genes, it is possible to clarify the role of immunologic and inflammatory mechanisms in atherosclerosis. Obviously, the findings in such models must be corroborated, as much as possible, by studies of human cells and tissues. Our current understanding of atherosclerosis therefore rests on a combination of research in animals and cell cultures, analysis of human lesions, clinical investigations of patients with acute coronary syndromes, and epidemiologic studies of CAD.

Lipoprotein retention and activation of immune cells. Role of Endothelial Activation, Adhesion Molecules, and Chemokines. Studies in animals and humans have shown that hypercholesterolemia causes focal activation of endothelium in large and medium-sized arteries. The infiltration and retention of LDL in the arterial intima initiate an inflammatory response in the artery wall. Modification of LDL, through oxidation or enzymatic attack in the intima, leads to the release of phospholipids that can activate endothelial cells, preferentially at sites of hemodynamic strain. Patterns of hemodynamic flow typical for atherosclerosis-prone segments (low average shear but high oscillatory shear stress) cause increased expression of adhesion molecules and inflammatory genes by endothelial cells. Therefore, hemodynamic strain and the accumulation of lipids may initiate an inflammatory process in the artery. The platelet is the first blood cell to arrive at the scene of endothelial activation. Its glycoproteins Ib and IIb/IIIa engage surface molecules on the endothelial cell, which may contribute to endothelial activation. Inhibition of platelet adhesion reduces evolution of the rupture-prone atherosclerotic plaqueleukocyte infiltration and atherosclerosis in hyper-cholesterolemic mice. Activated endothelial cells express several types of leukocyte adhesion molecules, which cause blood cells rolling along the vascular surface to adhere at the site of activation. Since vascular-cell adhesion molecule 1 (VCAM-1) is typically up-regulated in response to hypercholesterolemia, cells carrying counterreceptors for VCAM-1 (i.e., monocytes and lymphocytes)preferentially adhere to these sites. Once the blood cells have attached, chemokines produced in the underlying intima stimulate them to migrate through the interendothelial junctions and into the subendothelial space. Genetic abrogation or pharmacologic blockade of certain chemokines and adhesion molecules for mononuclear cells inhibits atherosclerosis in mice. Macrophages in the Developing Plaque. A cytokine or growth factor produced in the inflamed intima, macrophage colony-stimulating factor, induces monocytes entering the plaque to differentiateinto macrophages. This step is critical for the development of atherosclerosis and is associated with up-regulation of pattern-recognition receptors for innate immunity, including scavenger receptors and toll-like receptors. Scavenger receptors internalize a broad range of molecules and particles bearing molecules with pathogen-like molecular patterns. Bacterial endotoxins, apoptotic cell fragments, and oxidized LDL particles are all taken up anddestroyed through this pathway. If cholesterol derived from the uptake of oxidized LDL particles cannot be mobilized from the cell to a sufficient extent, it accumulates as cytosolic droplets. Ultimately, the cell is transformed into a foam cell, the prototypical cell in atherosclerosis.Toll-like receptors also bind molecules with pathogen-like molecular patterns, but in contrast to scavenger receptors, they can initiate a signal cascade that leads to cell activation. The activated macrophage produces inflammatory cytokines, proteases, and cytotoxic oxygen and nitrogen radical molecules. Similar effects are observed in dendritic cells, mast cells, and endothelial cells, which also express toll - like receptors. Bacterial toxins, stress proteins, and DNA motifs are all recognized by various toll-like receptors. In addition, human heat-shock protein 60 and oxidized LDL particles may activate these receptors. Cells in human atherosclerotic lesions display a spectrum of toll-like receptors, and plaque inflammation may partly depend on this pathway. In support of this notion, genetic removal of a molecule in the toll-like receptor signaling pathway inhibits atherosclerosis in apoE-knockout mice.

3.2.2.5

EPIDEMIOLOGICAL GENETIC STUDIES OF HUMAN TLRS AND IL-1RS. Epidemiological genetic studies

of infectious diseases assess the impact of human genetic variation on resistance or predisposition to infectious diseases, or the severity of these diseases, at the population level. These are typically population-based studies focusing on relatively common infectious diseases. This field is also known as the complex genetics of infectious diseases because it is generally assumed that susceptibility to common infectious diseases displays complex inheritance, which is often interpreted as polygenic inheritance. As discussed above, the seminal discovery in this field occurred in 1954: the ability of the HbS allele to protect against severe forms of malaria. This association study focusing on a candidate gene was followed by other studies, many of which were less successful. The most solid achievement of this approach in this field is probably the discovery of the lower risk of severe malaria in carriers of various erythrocyte traits, including the sickle cell trait, thalassemia, pyruvate kinase deficiency, and G6PD deficiency. By 1996, the first genome-wide linkage study had mapped a locus for susceptibility to Schistosoma mansoni infection, raising the possibility that major genes for infectious diseases exist within the population. Other genome-wide linkage studies mapping major loci followed, for diseases such as leprosy and tuberculosis. In leprosy, LD mapping of the two main linked regions on chromosomes 6q and 6p led to the identification of common risk variants in the PARK2/PACRG and LTA genes, respectively. However, it was not until 2007 that the first genome-wide association (GWA) study of an infectious disease was reported, in the form of an investigation of the genetic control of HIV-1 viral load. In this context, we review here the most significant candidate gene and genome-wide studies, which were all based on association (as opposed to linkage), that have provided insight into the role of TLRs, IL-1 cytokines, IL-1Rs, and molecules in their core TIR signaling pathway, including TIR-containing adaptors, in the development of infectious diseases.The possible role of genetic variants of members of the IL-1 and IL-1R families has been studied mostly in immune-mediated and inflammatory diseases such as arthritis, systemic lupus erythematosus, asthma, and atopic dermatitis as well as in cardiovasculardiseases. Relatively fewstudies have investigated the role of such variants in human infectious diseases, although IL-1 has been shown to play an important role in immunity to various pathogens in mouse models. In humans, many association studies have investigated the role of variants of IL1B, the gene encoding IL-1β, in Helicobacter pylori–related chronic atrophic gastritis and gastric cancer. IL-1β was previously shown to be upregulated in the presence of H. pylori, to play an important role in initiating and amplifying the inflammatory response to this infection, and to be a potent inhibitor of gastric acid secretion. Three biallelic polymorphisms in IL1B, all consisting of C-to-T base transitions, at positions −511, −31, and +3953 relative to the transcription start site, havebeen widely tested in association studies. The IL1B −511 and IL1B −31 SNPs are in almost perfect LD, and the rare alleles of these SNPs are associated with higher levels of IL-1β production in vitro and in vivo. The first study, conducted in two samples of Scottish and Polish ancestry, showed that subjects carrying the rare allele of both the IL1B −511 and IL1B −31 SNPs had a higher risk of gastric hypochlorhydria in the presence of H. pylori (a precancerous abnormality) and of gastric cancer. This association was subsequently confirmed by several other groups in populations of European, Hispanic, and Asian descent, although some discrepancies were reported that might be accounted for by the effects of interactions between population-specific genetic background, environmental factors (e.g., diet), and/or microbial strains. Consistent with this view, two studies reported a combined effect of these proinflammatory IL1B genotypes and H. pylori virulence factors, suggesting a possible interaction between the host and the bacterium in the development of gastric cancer. Further evidence for the role of IL-1β in these deleterious gastric effects comes from the recent description of transgenic mice with targeted IL- 1β overproduction in the stomach; the mice developed severe gastritis, dysplasia, and adenocarcinomas that could be prevented by the infusion of IL-1 receptor antagonist. These data suggest that proinflammatory IL1B genotypesleading to vigorous IL-1β production in response to H. pylori gastric infection may exacerbate mucosal damage and increase the risk of atrophic gastritis and gastric cancer. Tuberculosis has also frequently been investigated forassociation with genetic variants of IL-1 family genes, but these association studies provided no clear conclusions.A weak association between tuberculosis (pulmonary or extrapulmonary) and the IL1B +3953 SNP was reportedin three independent studies in Gujarati Indian (when combined with a variant of the IL1RA gene), Colombian, and African American patients, although the sample sizes were small and this association was not found in a largercohort from Cambodia. MAL, which is required for MyD88-dependent responses to TLR2 and TLR4, is the only TIR-containing adaptor investigated in association studies of infectious diseases. One study investigated the roleof several MAL SNPs in various infectious diseases and reported a role for the non-synonymous C539T (S180L) variant in protection against invasive pneumococcal disease (IPD), bacteremia, malaria, and tuberculosis. The frequency of the rare protective allele was approximately 2–3% in subjects from West and East Africa and Vietnam,and the protective effect was observed in heterozygotes (no homozygotes were observed in these populations). The allele frequency was higher in the UK (~16%), and although a protective effect was again observed in heterozygotes, a trend toward a deleterious effect was observed in subjects homozygous for the rare variant allele. This was interpreted as a heterozygote advantage effect of the S180L variant, which has been shownto be ancient in the West Eurasian region. However, the selective advantage conferred by this mutation, if indeed there actually is one, must have been weak and ancient, because population genetics has provided no firm

evidence supporting a role for natural selection in the distribution of this mutation. Furthermore, two additional studies failed to replicate this protective effect in a large sample of tuberculosis patients from Russia, Ghana, and Indonesia or in various samples of malaria, sepsis, and leprosy patients from Germany, Bangladesh, and Turkey. Another previous study also failed to detect a protective effect of S180L variation in tuberculosis patients from Vietnam. Overall, no convincing evidence of a heterozygote advantage associated with the S180L variant has yet been obtained, and the combination of samples of patients with infectious diseases as different as tuberculosis and malaria may not be the optimal strategy for dissecting the genetic basis of these diseases. It is possible that these diseases have similar genetic etiologies, but the pathways involved may have different effects in different diseases (e.g., a strong inflammatory response may be beneficial in tuberculosis and detrimental in cerebral malaria, or vice versa). What role do TLR variants play in human infectious diseases? TLR1 forms a heterodimer with TLR2 for the recognition of microbial triacetylated lipoproteins and mediates cell activation by Mycobacterium leprae. This finding led to several studies investigating the role of TLR1 and TLR2 variants in leprosy. For TLR1, the principal results were obtained with a nonsynonymous T1805G (I602S) SNP. Subjects who were GG (SS) ho-mozygous for this SNP had an impaired TLR1 response in several in vitro experimental systems and impaired TLR1 expression on the surface of monocytes, suggesting a defect in TLR1 trafficking. A study of the association of this polymorphism with leprosy was also carried out in a small Turkish sample of 57 leprosy patients and 90 controls, and GG (SS) homozygous subjects (frequency of 24% in the control population) were found to be protected against leprosy. The authors suggested that M. leprae may subvert theTLR system in an immune evasion mechanism. This association has not yet been replicated, but a study in a Nepalese population reported that leprosy patients who were TG (IS) heterozygous or GG (SS) homozygous at this SNP were protected from leprosyreversal reactions— acute episodes of immunologically mediated inflammation occurring during the course of the disease. The frequency of the TLR1-1805G (602S) allele varies considerably between populations and is highestin European populations (up to 75%), with this allele having a lower frequency in individuals of Turkish (~43%), African (~25%), Nepalese (~7%), and Vietnamese (~1%) origin. In a large sample from Bangladesh, the frequency of the TLR1-1805G (602S) allele was ~5%, and this allele was not found to be associated with leprosy or leprosy reactions, whereas these two phenotypes were weakly associated with another nonsynonymous TLR1 - A743G (N248S) SNP. One study also reported an association of some TLR2 variants with leprosy reversal reactions in an Ethiopian population. The non-synonymous C2029T (R677W) TLR2 variant, which had been associated with lepromatous leprosy in Korea, was subsequently shown not to be a true TLR2 polymorphism.TLR2 and TLR1 act together to mediate responses to Mycobacterium tuberculosis, and the role of variants in the corresponding genes in predisposition to tuberculosis has been investigated. Most studies have focused on TLR2 variants, and only weak and nonreplicated associations have as yet been reported. A nonsynomymous TLR2 -G2258A (R753Q) variant reported to increasethe risk of tuberculosis in a small Turkish sample was not associated with tuberculosis in European or Hispanic samples and was almost entirely absent fromAfrican and Asian populations. Another reported association between tuberculosis and an intronic TLR2 microsatellite was found in a Korean population but was not replicate d in a Chinese popula tion. A study in Vietnam re porte d an assoc iation betwee n a synonym ous TLR2 -T597 C (N199N) variant and meningeal tuberculosis caused by the East Asian/Beijing strain, but this association has yet to be confirmed. Another study investigated the role of variants in several TLRs, through full exon sequencing for TLR1,TLR2, TLR4, TLR6, and TLR10 (TLR4 andTLR6 have also been implicated in the recogition of mycobacterial antigens, and TLR1,TLR6, and TLR10 are located in a single gene cluster) in three samples of tuberculosis patients and controls of African American, European, and Hispanic origin. No association with TLR2 polymorphisms was found, but the authors reported an excess of rare nonsynonymous variants of the TLR10-TLR1- TLR6 cluster in African American tuberculosis patients. In addition, African American patients homozygous for the common TLR1-1805T (602I) allele were found to be at higher risk of tuberculosis, and the 1805T allele was in LD with the 743G allele (248S) of the nonsynonymous TLR1-A743G SNP [the pattern of LD was different from that in the Bangladeshi sample] and with another nonsynonymous TLR6SNP (S249P). However, a recent study investigating the role of several SNPs tagging TLR1 (including N248S) and TLR6 (including S249P) in samples of African American, Caucasian, and African (Guinea-Bissau) origin found no association of tuberculosis with TLR1 or TLR6 polymorphisms, whereas an association with an-other TLR2 variant was observed. Finally, a cluster of four TLR8 SNPs (includinga non-synonymous variant affecting TLR8 isoform B) was associated with pulmonary tuberculosis in male patients from Indonesia and Russia. This interesting result merits further investigation, as TLR8 is on the X chromosome and pulmonary tuberculosis is more frequent in men than in women. Variants of other TLR genes, such as TLR4, have also been reported to be involved in tuberculosis in some studies, but these findings have yet to be replicated. Overall, the role of TLR variants (with possible interactions between several TLRs, such as TLR1and TLR2) in the two main mycobacterial diseases, leprosy and tuberculosis, remains unclear. Further studies are required. Not only does TLR recognize mycobacterial products, but it is also involved in the recognition of a widerange of molecules from bacteria, fungi, parasites, and viruses. Several association studies have investigated

therole of TLR2 variants in various infections, but these studies generated no firm conclusions. Most focused on the nonsynonymous G2258A(R753Q) SNP identified in tuberculosis studies, as the 753Q variation decreases the ability of TLR2 to respond to bacterial peptides in vitro. Perhaps one of the most interesting associations with this polymorphism was observed in Borrelia burgdorferi infections, with the TLR2-2258A (753Q) variant having a protective effect against late-stage Lyme disease in European subjects, although this is the only study to date to have investigated the role of TLR2 variants in Lyme disease. This suggests that a decrease in signaling via TLR2 may protect against late clinical manifestations of Borrelia infections, which may be at least partly the result of inflammation. However, in another study of 75 patients with Salmonella enteritidis infection, the 753Q variant was associated with a higher risk of acute reactive arthritis following infection. Finally, the potentially deleterious effect of the TLR2-753Q variant, associated with septic shock in gram-positive infections, especially those caused by Staphylococcus aureus, was not confirmed in a larger study. TLR4 is the key receptor for the LPS component of gram-negative bacteria and is also involved in the recognition of structures from mycobacteria, fungi, and malaria parasites. The TLR4 gene has two main nonsynonymous SNPs, A896G (D299G) and C1196T (T399I), which are in strong LD in European populations but not in African populations and are almost absent from Asian populations. Studies on these SNPs have focused on heterozygous subjects, as few subjects homozygous for the rare allele have been found. Conflicting results have been obtained concerning the functional impact of these variants, with some in vivo studies showing that these TLR4 variants are associated with hyporesponsiveness to inhaled LPS in humans, whereas most in vitro studies have shown that cells from individuals heterozygous for the 896G (299G) allele respond to LPS in a manner similar to cells from subjects homozygous for the wild-typeallele. Several association studies investigating the role of these TLR4 variants in various infectious diseases have yet to provide conclusive results, either because they generated conflicting findings, as for sepsis and respiratory syncytial virus infection, or because they were based on a single study, as for severe malaria or Legionnaires‘ disease. In meningococcal meningitis, the 299G variant has been associated with a fatal outcome, particularly in young children (<2 years of age), whereas no effect of this variant was observed when total samples of children and/or adults were considered. An interesting study based on systematic sequencing of the coding regions of TLR4 in a sample of patients with meningococcal sepsis (<18 years of age) also found no association of the disease with the 299G (and 399I) variant, but this study did report an excess of some other rare heterozygous missense TLR4 mutations in these patients and a trend toward a stronger association with the subgroup of patients who died. Finally, an interesting study reported that invasive aspergillosis in the recipients of allogeneic stem cell transplants was associated with the TLR4-896G- 1196T (299G-399I) haplotype of the donor cells (when the donor was unrelated to the patient) but not with that of the recipient. This finding has yet to be confirmed but is consistent with another study reporting an association of the TLR4-299G variant with chronic cavitary pulmonary aspergillosis. The mechanism underlying this association remains unclear, as no ligand from Aspergillus fumigatus has yet been identified. Thus,TLR4 may have an indirect effect by modifying the bacterial flora colonizing these patients, thereby influencing fungal colonization and immunity to fungi.

3.2.2.6

1. Radiosensitivity

Radiosensitivity is the relative susceptibility of cells, tissues, organs or organisms to the harmful effect of ionizing radiation.

Cells types affected

Cells are least sensitive when in the S phase, then the G_1 phase, then the G_2 phase, and most sensitive in the M phase of the cell cycle. This is described by the 'law of Bergonié and Tribondeau', formulated in 1906: X-rays are more effective on cells which have a greater reproductive activity.

From their observations, they concluded that quickly dividing tumor cells are generally more sensitive than the majority of body cells. This is not always true. Tumor cells can be hypoxic and therefore less sensitive to X-rays because most of their effects are mediated by the free radicals produced by ionizing oxygen.

It has meanwhile been shown that the most sensitive cells are those that are undifferentiated, well nourished, dividing quickly and highly active metabolically. Amongst the body cells, the most sensitive are spermatogonia and erythroblasts, epidermal stem cells, gastrointestinal stem cells. The least sensitive are nerve cells and muscle fibers. Very sensitive cells are also oocytes and lymphocytes, although they are resting cells and do not meet the criteria described above. The reasons for their sensitivityare not clear.

There also appears to be a genetic basis for the varied vulnerability of cells to ionizing radiation. This has been demonstrated across several cancer types and in normal tissues.

2. Radiosensitivity

Radiosensitivity is the relative susceptibility of cells, tissues, organs or organisms to the harmful effect of ionizing radiation.

Cell damage classification

The damage to the cell can be lethal (the cell dies) or sublethal (the cell can repair itself). Cell damage can ultimately lead to health effects which can be classified as either Tissue Reactions or Stochastic Effects according to the International Commission on Radiological Protection.

Tissue Reactions

Tissue reactions have a threshold of irradiation under which they do not appear and above which they typically appear. Fractionation of dose, dose rate, the application of antioxidants and other factors may affect the precise threshold at which a tissue reaction occurs. Tissue reactions include skin reactions (epilation, erythema, moist desquamation), cataracts, circulatorydisease, and other conditions.

Stochastic effects

Stochastic effects do not have a threshold of irradiation, are coincidental, and cannot be avoided. They can be divided into somatic and genetic effects. Among the somatic effects, secondary cancer is the most important. It de velops beca use ra dia tion causes DNA m utations directly and indirectly. Direc t effects are those ca use d by ionizin g particles and rays themselves, while the indirect effects are those that are caused by free radicals, generated especially in water radiolysis and oxygen radiolysis. The genetic effects confer the predisposition of radiosensitivity to the offspring. The process is not well understood yet.

3. Radiosensitivity

Radiosensitivity is the relative susceptibility of cells, tissues, organs or organisms to the harmful effect of ionizing radiation.

Cell damage classification

The damage to the cell can be lethal (the cell dies) or sublethal (the cell can repair itself). Cell damage can ultimately lead to health effects which can be classified as either Tissue Reactions or Stochastic Effects according to the International Commission on Radiological Protection.

Target structures

For decades, the main cellular target for radiation induced damage was thought to be the DNA molecule.This view has been challenged by data indicating that in order to increase survival, the cells must protect their proteins, which in turn repair the damage in the DNA. An important part of protection of proteins (but not DNA) against the detrimental effects of reactive oxygen species (ROS), which are the main mechanism of radiation toxicity, is played by non-enzymatic complexes of manganese ions and small organic metabolites.

3.2.2.7

1. Radon and Radioactivity

What is radon

Radon, more exactly radon-222, is a natural radioactive inert gas, that is colourless and tasteless, without any chemical reactions in the human body. It has a high alpha radiation energy, but a small penetration depth up to 4 tissue cells. This high energy alpha-radiation causes biological effects in the cells. Thus low doses, as we use it in radon balneology, induce positive biological effects as described below, whereas high doses causes damage to the cells. Radon is everywhere in the earth crust and mainly concentrated in granite mountains, that‘s why radon spas are located in such regions

Radon (Rn) 222 is generated from Radium (Ra) 88, which is derived from uran over millions of years. The physical half-life of radon is 3,8 days, whereas the biological half-life is only 20 - 30 minutes. Thus half of the radon intake has left the body within this time. Only few hours later no radon can be verified in the body anymore.The discussion about ra don-risk does not c oncern ra don itself, but m ostly its ―da ugthe rs‖, whic h mea ns its de gra dation products, especially polonium, bismuth and plumbum with short physical half-lifes between 162 msecand 26,8 min (Po 214 and Pb 214). These reactive „daugthers‖ are estimated about only 2 %, whereas the main portion, the inert radon, leads to no chemical reactions in the body. Within hundreds of years of radon balneology no specific negative side-effects, especially tumorgenesis, have been described. In contrary, lowradiation, as we use it in radon balenolgy leads in experimental animal studies to positive effects in regeneration and repair of cells.

2. Radon and Radioactivity

Which biological effects ofradioactivity are known

In the case of ionizing radioactivity, energy is transmitted, which triggers particular changes in cells in the human body. Radiation experts are agreed that exposure to large doses of radioactivity can cause cancer or harm unborn children in their mother's womb.

However, experts do not conformonthe risk to health posed by very lowdoses of radioactivity.
There is re lia ble e vide nce from a nimal e xpe rime nts, epidemiological a nd oberserva tion-studies, e xperime nts carrie d out on animals and studies involving human beings, that radioactivity in tiny doses up to a particular presumable threshold can even be beneficial to people's health. Balneologists assume that small doses of radiation in the form of radon provide a short stimulus, which animates cells and organs. This positive effect of small doses,as opposed to the damaging effect of large doses, is called hormesis (hormao - Greek "to stimulate, excite"). This hormesis theory contrasts with the theory of a linear dose-effect relationship(LNT)without any threshold. Purely for precautionary reasons, the German Office for Radiation Protection maintains the view that radiation even in very small doses might still be dangerous.
However, this is a purely theoretical assumption, as it is only based on calculations. Up to now no evidence has been provided suggesting that any danger to people's health is posed by radioactivity in small doses.

3. Radon and Radioactivity

How is radon therapy carried out

Taking baths, drinking, inhaling - these are the three different types of radon therapy practised at spa centres nowadays during two-, three- or four-week spa treatments with loading doses in 8 to 12 applications. The inert gas penetrates mainly the body's skin during serial radon baths.
Additional inhalation of radon gas on the water surface is possible. To improve skin absorption and to protect the lung we often us bathtubes covers. During spa treatments in a therapeutic mining gallery, patients breathe in air containing radon. If the patients are naked, radon is also absorbed via the skin. At centres with springs containing radon, the rising gases can also be trapped and fed to the patients via domes, so that they can inhale the mix, or to cubicles for steam baths.
In the case of treatment where water containing radon is drunk, the person's blood circulation absorbs radon via the stomach / digestive tract.

3.2.3 Тексты для аудирования

3.2.3.1

In the last lectures we have learned that kidney transplantation is the preferred option for patients with end stage renal disease. It was also discussed that patients need lifelong medication to suppress the immune system. Indeed, kidney transplantation in the absence of immunosuppressive drugs is only possible if and recipient are monozygotic twins. In all other situations, transplantation leads to immunological graft rejection. This is a clear indication that genetically determined components play a crucial role. The main targets for graft rejection are human leukocyte antigens, known as HLA. In this lecture you will learn about the definition of HLA. In addition, you will be familiar with the assays used to type for the HLA antigens. At the end of the lecture, you will be able to explain why the chance to find an HLA identical unrelated donor is far more difficult than finding an HLA identical donor in the family of the patient.
Let us start with the very beginning. In 1954, Jean Dausset in Paris observed that sera obtained from patients after blood transfusion were able to agglutinate white blood cells. Until that time agglutination of red blood cells was the way to type for the ABO blood group antigens. He calls the antigens recognized human leukocyte antigens, or briefly HLA. A few years later Jon van Rood in Leiden, and Rose Payne in Stanford, found similar antibodies in the sera from women after pregnancy. It became soon clear that there are many different HLA antigens and that these antigens play a role in transplantation. Pregnancy sera were considered excellent reagents for HLAtyping, but the problem was that this agglutination essay was very cumbersome. Serological HLA typing became a routine procedure after the introduction of the microcytotoxicity assay by Paul Terasaki. The advantage of this assay was that only one microliter of serum could be used, which makes it possible to many HLA typings with thesame serum sample. For many years HLA typing was performed by testing the reactivity of many pregnancy sera with different antibody specificities against the lymphocytes of an individual. So how does the procedure of serological HLA typing work? In every well of a so-called Terasaki tray, a different serum is present. Lymphocytes of the person to be typed are added to these sera. This lymphocytes express all HLA antigens, which this person has inherited. If the serum contains antibodies which recognize these HLA antigens, the antibodies will bind to the lymphocytes. Addition of complement will result in lysis of the lymphocytes, which is visualized by a red dye. If a serum does contain antibodies which do not recognize HLA antigens of this person, the antibodies will not bind to the lymphocytes and addition of complement will not affect the viability of the cells. The problem with serological HLA typingwas the fact that it was not possible to standardize the reagents which were sera from pregnant women. Therefore, serological HLAtyping has gradually been replaced by molecular HLA typing. As the HLA antigens are genetically determined it is possible to develop reagents to characterize the genes coding for the HLA molecules on the cell. The advantage of molecular typing is the fact that the reagents are standardized. And that the analysis

provides more details on the HLA molecules compared to serological typing. Introduction of molecular typing has led to an enormous increase of the number of different HLAalleles.
Let us look now at the genetics of HLA. All genes coding for the HLA antigens are clustered on the short arm of chromosome 6. There are two types of HLA molecules, called HLAclass I and HLA class II. They have a different tissue distribution and a different function, which will be discussed later in this course. The genes coding for HLA class I are called HLA A, B, and C. The genes coding for HLA class II are called HLA DR, DQ, and DP. Every individual has two sets of HLAgenes, one inherited from the father, and one inherited from the mother. Theproducts of all these HLA genes are expressed on the cell surface. Considering the genetic complexity of HLA and the high number of HLA alleles, you can wonder how can one select an HLA identical donor for a particular patient? In the family situation the chance to find an HLA identical donor is about 25%. As mentioned before the HLA genes are clustered on the short arm of chromosome 6. And everybody inherits one set of HLA genes from the father, and one from the mother. Such a set of HLA genes is called an HLA haplotype. In principle, there are only four different combinations of HLA haplotypes possible, leading to a chance of 25% to have an HLA- identical brother or sister. In case of unrelated donors, this chance is much lower, due to the very high number of HLA antigens, and the fact tha t everybody has two sets of HLA antige ns expresse d. In this slide, the c urre nt num ber of HLA a ntige ns is shown. If one would randomly choose two out of the 1740 HLA-A alleles, and two out of the 2329 HLA-B, and so on, the chance that two individuals will have the same HLA type will be very low. Fortunately, the frequency of some of these HLA antigens is rather high. Furthermore, certain HLA haplotypes occur more frequently than expected on the basis of the frequency of the individual alleles. Therefore, it is certainly possible to find an HLA identical donor for a proportion of the patients provided that the potential donor population is large.
You have now seen that HLA antigens are the main targets for graft rejection. And that both serological and molecular assays can be used for HLA typing. Finally the chance to find an HLA identical unrelated donor is far more difficult than finding an HLA identical donor in the family of the patient. In the next lecture, we will look at the natural function of the immune system which is of importance to understand the principles of graft rejection.

3.2.3.2

So hello, welcome. I'm here for this antimicrobial resistance lecture, this time on selection. My name is Lina Cavaco and I have a very interesting presentation about this selection issue. In the previous lectures you have heard about how resistance happens and how it can spread around. And here, selection would be how can it really be a bigger problem, how this problem can grow. So we'll look into that more in detail. I'll have some introductionabout what this selection and selection of resistance as such, and how a bacteria can be even multidrug resistant.So and then come in the news as a big, big threat and issue. And how a little bit of about the history of emergence and now we have been talking about single bacterias. I'll also bring it just a touch up on that bacteria sometimes are not alone and they are together in a society. So to start with, well, many of you have heard about Charles Darwin and that he figured out how we evolve and how we are selected naturally so that the best ones survive and go ahead. In bacteria it is quite similar. So if they are adapted to the environment and if they can survive better, they will be fittest and they will survive. So also in antimicrobial resistance, that's what happens. The best ones,the most resistant ones are the ones that can survive to the environment. So we can think of selection theoretically as something that happens well. We have these bacteria, they are normal, they are growing around in the environment. Or maybe in an animal or in a human, it doesn't matter. They are dividing, and suddenly one of thesebacteria became resistant. Let's say it became resistant by a mutation. It could be by a resistant gene. It doesn't matter in this case, but it became more resistant than the others. Here in this environment they are living happily and they don't have any antimicrobials. But, let's say that some point they are transferred into this environment that has antibiotics. Suddenly only the green ones survive. So the blue ones are dead, they are not there anymore, and the green ones take all the space. So suddenly, it's a big advantage to be green. And that's what selection is about. And when we talk about reduction of use of antimicrobials when it's not necessary. For example if you havea flu that you should not take antibiotics it's to avoid this. To avoid that bacteria become or select to be resistant even when it's not necessary. So if we take, for example, now we have two populations of bacteria, the blue ones and the green ones. The green ones have some resistance genes, but they are living in the place where it's not really necessary. But because they are in the same population they might have some contact with each other. And because they have some contact with each other way, one of the round ones become green because it's acquired this resistance determinant. But it doesn't really need it. But once there is some selective pressure, and this is a definition that we also need to give, that is, for example, an environment where antimicrobials are present. And give some pressure towards the resistance, so that the pressure makes that the resistance is an advantage. Suddenlybeing green is an advantage. So also the blue ones become green more often. Because the blue ones might be dying under that pressure. So the key word in this is selection. If we have a resistance level that is low and there is some antimicrobial in the environment or in the animal or in the human, there is some treatments going on, the

tendencies get higher and higher. So that's why in countries we measure resistance and we look at, is it getting higher, is it getting worse? Do we get still people treated with these antimicrobials? And we start to worry once it gets worse. So and here we have one thing that if it can get worse, it will. It's the law of Murphy in a way. So if we have resistance going on and there's more and more use, you get the same bacteria maybe getting even more resistant genes, and more resistant genes, and it will get worse and worse. So there's kind of a snowball effect. And if we keep on using a lot of antibiotics, it might be that at some point we don't have possibilities for treatmentbecause it gets worse and worse in the bacteria. And, we don't want it to get here, but, unfortunately, I must tell you that some bacteria are really so difficult to treat that there is almost no antimicrobial to treat them. If we go really back, we had only plants to do some treatments. If you go a little bit then there were some that making potions out of these plants. Then in 1941, that's where penicillin came into the market. It was discovered a few years before. Then they say well potions are quite poisonous. We have antibiotics that are better and then don't cause so much problem to the person tha t ta kes them. Let's ta ke pe nic illin. The n other scie ntist found ma ybe some bacteria are getting resistance. Other drugs are being found. Let's take other drugs. And then, it happens that some are resistant now to this one too, let's take a new one. And it went on with new one and new ones. Now for a few years, we don't really have many new ones. They haven't been discovered many. So we hope we don't get there. If we many oops later need to eat the plant again, I hope not. But sometimes in the hospitals it's already there that doctors don't really have many choices anymore or almost no choices anymore. So this is to give you an idea about bacteria as one. But we haven't talked about societies. Sometimes bacteria are together in a, living together on a surface or living together in a society where they are quite structured. They're not only living for themselves. And here they are not only acting for themselves and having their own resistance. They also have some resistance as a group. So actually in this situation they might have some modifications. And they might have some stress responses and cells that are becoming more persistent and more adapted. And actually the tendency is if they are in these biofilms and in the societies they're actually more resistance to the action of drugs. So it's more difficult toget rid of a bacteria that are in this situation. So that's why sometimes we have hospital infections due to bacteria in a certain surface or in catheters for example. So this is also something that the doctors worry quite a lot about, about the biofilms and the bacteria as a society. Thank you very much. That was it for selection. Another good thing about selection is, if we don't use it as much, if we turn down the use, we can still have antibiotics for a little longer time at least. So that's why we also worry about that. Thank you very much, and see you for the next lecture.

3.2.3.3

Now that we know a little bit about how to look at microbial sequence data, we'll discuss some of the factors that determine what someone's gut microbiota looks like. The main factors that influence the gut microbiota are age, diet, antibiotic use, genetics and physiology. Yeast factors change the gut microbiota by changing the selective environment in the gut. What does that mean? Although we can gain new gut microbes during our life, most of the changes that occur are changes in the relative abundances of the microbes that are already in our guts. Basically, we end up having more or less different kinds of bacteria. Imagine you have lots of microbes in your gut that like warm places, and only one or two microbes that prefer cold places. Suddenly your gut becomes colder. After a while, you should only have a few of the microbes that like warmth, but many that like the cold. Although your gut doesn't change temperature much, this is exactly how age, diet, antibiotics, genetics, and physiology affect your gut microbes. They change the environment that the microbes are living in. So that's how they do it, but whatexactly do they do? Let's talk about each of these factors individually. We'll start with age. Based on Jessica's lecture during week one, we know that we start with a mostly sterile gut, and start accumulating microbes during and after birth. Therefore, infants and babies have low gut microbial diversity. The gut microbiota can also changedramatically from one day to another as babies come into contact with new people and foods and gain more microbes. Remember the animation that we watched. At about one year of age, our gut microbial communities aremuch more diverse then when we were born, but they continue to develop as we eat more solid foods and explore the world around us. Our gut microbial community become more diverse and more stable as we become adults. Once we reach adulthood our microbial communities are highly complex and they stay that way for the rest of our lives. However, studies have shown that as we move into old age we begin to lose some of the stability that we had as younger adults. The composition of our gut microbial communities becomes more variable again from day to day and week to week. The changes we see in our gut microbiota with age are much like the changes we see in other aspects of our bodies, like our skin, eye sight, memory, and immune system. Although we don't fully understand all the microbiome changes that occur in old age, they are natural processes that are likely difficult to alter. We can influence other impacts on the gut microbiota, though. Diet is a great example. Both your long term diet habits, as well as short term changes in your diet, can lead to shifts in the kinds of microbes that you have. And as anyone that has ever been on a diet will tell you, while it may be difficult, you do have control over what we eat. Let's address the long term impact of diet on the gut microbiota first. A study by Gary Wu and

collaborators show that the general diet a person consumes over a year is strongly correlated with the composition of the gut microbiota. In this study, people who ate a lot of carbohydrates, things like pasta, potatoes, and sugars, tended to have a lot of prevotella bacteria, which you can see in the figure on the right. While people who ate a lot of protein, especially meat, tended to have a lot of bacteroides, which you can see on the left. An examination of microbiota across nations and cultures, by Yatsunenko and collaborators, resulted in similar patterns. Africans from Malawi, who eat mostly corn, and Amerindians from Venezuela, who eat mostly cassava, also had a lot of privatella compared to people in the US and Europe who eat more meat and processed foods. You can see how their gut microbes separate on this plot. Based on these two studies, it seems that if your diet falls into a specific category, your microbes will fall into a category as well. However, short term changes in diet also have an effect on the gut microbiota. In Wu's study, people that were fed a controlled diet that differed from their normal diet for ten days experienced rapid changes in the abundances of different microbes in the gut. On the right, you can see how the dissimilarity between the samples of one person is high between day one and the other days as diet changes. These are the blue columns. Even so, you can see on the left that every person, represented by a differentcolor, had a gut microbiota that still looked more like their original microbiota than like that of someone else. Thismeans the observed changes were relatively minor. But a recent study by Turnbow and colleagues has demonstrated that a more extreme diet change can lead to more extreme microbiota changes over a short time. In this study, volunteers changed their diet dramatically for three days. Some volunteers went vegan, this is the left column of the graphs, and some ate a meat and cheese only diet, these are the right columns of the graph. The firstthree rows here show you fiber, fat, and protein intake for people on each diet over time. In the last row, you can see the changes in beta diversity or gut microbial community composition. The vegan diet caused a little change, but the meat and cheese diet caused big changes, almost over night. Specifically, there was an increase in bacteria linked to cardiovascular disease like hemophela. Although we still don't know enough about how specific parts of our diet interact with specific microbes to be able to prescribe diets that alter the microbiome and ultimately improve our health, these baseline studies suggest that this type of intervention could become a reality someday. Although diet has one of the largest known impacts on the gut microbiota, antibiotics can also change the gut microbiota dramatically. Antibiotics stop bacteria from doing things, like making proteins, dividing, making cell walls, and transporting nutrients. They can also put holes in cell walls or membranes. Needless to say, none of these things are good for the bacteria, so most bacteria die when they are exposed to antibiotics. As a quick side note, bacteria can evolve to be immune to the effects of antibiotics, something we call antibiotic resistance. This isa serious problem in medicine currently, since it makes us vulnerable to pathogenic bacteria that can't be stopped.I won't talk about that here, but Rob talks about it more in his book if you're interested. Antibiotics target bacteria, but they don't target pathogenic bacteria. They generally kill all bacteria in their path. Therefore, you can imagine what happens to your gut microbiota if you take an antibiotic to stop an infection you have from pathogenic bacteria. Your good bacteria will suffer too. That being said, difference types of antibiotics have different effects on your gut microbiota, and different people react differently to antibiotic use. For example, Dethlefsen and colleagues did a study where they gave three people the same round of the same antibiotic. They took samples from each person before giving the antibiotics and afterwards for one year to see what happened to the gut microbiota. You can see the data here. The gray lines indicate an antibiotic series. The gut microbiota changed in every person, but each person took a different amount of time to recover back to the original gut microbiota. One person bounced back almost immediately, another took a few weeks, and the third took a whole year, and even then didn't look quite the same again. If that wasn't interesting enough, Dethlefsen and colleagues continued the study by giving a second dose of antibiotics. Everyone showed a shift in their gut microbiota again, but this time the changes were mostly permanent. So although the effect can vary, antibiotics have a big effect on the gut microbiota. The moral of the story is to take antibiotics when you're sick, but make sure you're sick and that an antibiotic will help before you take them. To counteract the effects of antibiotics, and to alleviate gastrointestinal disorders, like diarrhea and intestinal bowel disease, many people have started to take probiotics. Probiotics are live microorganisms that benefit health when they're administered in sufficient quantities. Probiotics are found in dietary supplements, yogurts and even suppositories. Some have a single strain of bacteria while others have multiple strains. And still, others contain fungal microbes. Although many people take probiotics, we still don't know a lot about them and how they work. Basic research, as well as clinical trials, are currently happening for a number of different probiotics. In the meantime, we know that probiotics appear to be helpful for alleviating the symptoms of diarrhea, intestinal bowel disease, and other gastrointestinal disorders. There's also preliminary evidence that probiotics could be effective against obesity or mood disorders, but we still have a lot to learn beforewe can say any of this definitively. In addition to environmental factors like diet and antibiotic use, our genetics may also impact the gut microbiota. However, studies examining the effects of our genes on our microbiota have had mixed results, and many of the observed patterns are subtle. Twin studies are often used to understand the importance of genetics versus the environment in determining patterns we see in factors like disease. Take heart disease for example. Remember, monozygotic twins come from the same egg and therefore, have the same DNA,

while dizygotic twins do not. The idea is that if monozygotic twins both have heart disease more often than dizygotic twins both have heart disease, genetics is likely playing a role. In contrast, if both monozygotic and dizygotic twins have heart disease equally often, lifestyle factors, like diet and exercise, are more likely to be the main influencing factors. A similar approach has been used for studying the microbiome as well. The idea is that ifmonozygotic twins have microbiomes that are more similar to each other than dizygotic twins, genetics must be playing a role. Sounds simple, right? Unfortunately, the data from these studies has not been simple at all. Some studies have shown that monozygotic twins are more similar to each other, while others have not. The data are conflicting. Another approach to determining how genetics might be influencing the gut microbiome is to put individuals with different genetics into similar environments and see if their microbes become similar to each other. If they do, environment is more important. If they don't, genetics are more important. These types of experiments would be difficult, and potentially unethical with humans. But there have been a fewexperiments of this type with mice. In one, mice were placed with a different mother after birth. This mother had different genes than the mouse pup, but even so, the pup ended up looking more like the surrogate mother than its biological mother, in terms of the gut microbial community composition. This suggests that environment is more important than genetics in determining the gut microbiome. Nevertheless, studies that look at the particular genes present in individual mice and people, have shown that the presence or absence of a single gene can change the relative abundance of specific kinds of bacteria in the gut. This is particularly true for genera and species of bacteria. Genepresence or absence doesn't appear to have as much influence on the relative abundances of bacteria at higher taxonomic levels such as the phylum. For example, lactobacillus relative abundances have been shown to vary with host genotype in studies of mice. Also, many of the gene microbe interactions that have been detected involve immune function. For instance, humans with mutations in the MEFV gene get mediterranean fever and auto immune disease. And these individuals also show changes in the gut microbiome. Similarly, mice without TLR5 gene function, which impacts immune function, have distinct gut microbiota. Many of the bacteria that havebeen found to be influenced by host genetics, are also known to effect immune system function. So it seems that while the impact of host genetics on the gut microbiota may be more limited than the impact of other factors, it does exist. The last major factor influencing the gut microbiota is our physiology. This refers to factors like hormone levels, immune system function, metabolism, et cetera. All of these things can both affect, and be affected, by our gut microbiota, and likely interact with the other factors we've discussed. Instead of talking about that now though, we'll talk about that in separate lectures this week and next week. Because the interactions between our gut microbes and our body are numerous and complex, it will take some extra time to explore them.

3.2.3.4

1. International guiding principles for biomedical research involving animals (1985)

BASIC PRINCIPLES

I. The advancement of biological knowledge and the development of improved means for the protection of the health and well-being both of man and of animals require recourse to experimentation on intact live animals of a wide variety of species.

II. Methods such as mathematical models, computer simulation and *in vitro* biological systems should be used wherever appropriate.

III. Animal experiments should be undertaken only after due consideration of their relevance for human or animal health and the advancement of biological knowledge.

IV. The animals selected for an experiment should be of an appropriate species and quality, and the minimum number required to obtain scientifically valid results.

V. Investigators should never fail to treat animals as sentient, and should regard their proper care and use and the avoidance or minimization of discomfort.

VI. Investigators should assume that procedures that would cause pain in human beings cause pain in other vertebrate species.

VII. Procedures with animals that may cause more than momentary or minimal pain or distress should be performed with appropriate sedation, analgesia, or anesthesia in accordance with accepted veterinary practice.

VIII. At the end of, or, when appropriate, during an experiment, animals that would otherwise suffer severe or chronic pain, distress, discomfort, or disablement that cannot be relieved should be painlesslykilled.

X. The best possible living conditions should be maintained for animals kept for biomedical purposes. Normally the care of animals should be under the supervisionof veterinarians having experience inlaboratoryanimal science.

2. International guiding principles for biomedical research involving animals (1985)

SPECIAL PROVISIONS

1. Acquisition
Specialized breeding establishments are the best source of the most commonly used experimental animals. Nonspecifically bred animals may be used only if they meet the research requirements, particularly for health and quality, and their acquisition is not in contradiction with national legislation and conservation policies.
2. Transportation
Where there are no regulations or statutory requirements governing the transport of animals, it is the duty of the director of an institute or department using animals to emphasize to the supplier and the carrier that the animals should be transported under humane and hygienic conditions.
3. Housing
Animal housing should be such as to ensure that the general health of the animals is safeguarded and that undue stress is avoided. Special attention should be given to the space allocation for each animal, according to species, and adequate standards of hygiene should be maintained as well as protection against predators, vermin, and other pests. Facilities for quarantine and isolation should be provided. Entry should normally be restricted to authorized persons.

3. International guiding principles for biomedical researchinvolving animals (1985)
SPECIAL PROVISIONS

1. Environmental Conditions
Environmental needs such as temperature, humidity, ventilation, lighting, and social interaction should be consistent with the needs of the species concerned. Noise and odour levels should be minimal. Proper facilities should be provided for the disposal of animals and animal waste.
2 Nutrition
Animals should receive a supply of foodstuffs appropriate to their requirements and of a quality and quantity adequate to preserve their health, and they should have free access to potable water, unless the object of the experiment is to study the effects of variations of these nutritional requirements.
3. Veterinary Care
Veterinary care, including a programme of health surveillance and disease prevention, should be available to breeding establishments and to institutions or departments using animals for biomedical purposes. Sick or injured animals should, according to circumstances, either receive appropriate veterinarycare or be painlessly killed.
4. Records
Records should be kept of all experiments with animals and should be available for inspection. Information should be included regarding the various procedures which were carried out and the results of post mortem examinations if conducted.

3.2.4 Тематика для краткого сообщения

Краткое сообщение – продукт самостоятельной работы студента, представляющий собой краткое (5 минут) публичное выступление на английском языке по предложенной им самим теме, связанной с актуальным исследованием в какой-либо научной области биомедицины.

Примерные темы для кратких сообщений

1. Rest no substitute for sleep when learning.
2. Did sleep precede the brain?
3. Some bacteria know the time.
4. Some microbes could help treat type 2 diabetes.
5. Understanding how gut bacteria are connected to depression.

3.2.5 Итоговое задание для зачёта

Составьте текст на английском о себе и своей научной работе в соответствии с планом:

1. Образование.
2. Текущая рабочая и учебная деятельность.
3. Тема научной работы.
4. Ваш научный руководитель и консультант.
5. Актуальность Вашего исследования.
6. Цель и главные задачи исследования.
7. Объект и предмет исследования.
8. Материал исследования (содержание практической части научной работы).
9. Основные методы научного исследования.
10. Достигнутые результаты (публикации, выступления на конференциях и т. п.).

4. ПОРЯДОК ПРОВЕДЕНИЯ И КРИТЕРИИ ОЦЕНИВАНИЯ ПРОМЕЖУТОЧНОЙ АТТЕСТАЦИИ

4.1 Порядок проведения промежуточной аттестации

Итоговый контроль по дисциплине проводится по системе зачёт/незачёт по результатам представления зачётного задания и при наличии удовлетворительной текущей успеваемости (выполнение всех предусмотренных заданий на оценки не ниже 3 баллов и посещение не менее чем 90% всех занятий). Во втором случае (удовлетворительная текущая успеваемость) зачёт выставляется автоматически без представления итогового задания. При наличии недочётов (долгов) в текущей успеваемости помимо итогового задания студенту дополнительно предлагается выполнить перевод текста по биомедицинской тематике (см. раздел 3.2.2), который студент должен выполнить на оценку не ниже 3 баллов.

4.2 Критерии оценивания промежуточной аттестации по видам оценочных средств

4.2.1 Критерии оценивания зачётного задания

«Зачтено» – студент способен структурировано и логично представить итоговое задание, ясно и кратко излагает ответы на уточняющие вопросы; свободно и грамотно излагает свои мысли на английском языке. Допускаются небольшие погрешности и/или неточности в изложении.

«Не зачтено» – итоговое задание, представленное студентом, характеризуется несвязностью и отсутствием какой-либо структуры; студент допускает грубые ошибки грамматического и фактического характера.

4.2.2 Критерии оценивания перевода научного текста

№ п/п	Оцениваемый параметр		Баллы
1	Грамотность русского текста перевода	нет нарушений грамматики и стилистики	5
		есть незначительные нарушения грамматики и стилистики, не влияющие на целостность изложения	4
		имеющиеся грамматические и стилистические ошибки нарушают стройность текста в отдельных местах	3
		текст носит эклектичный характер, связи между отдельными частями и логика изложения нарушены	2
2	Научность перевода	научные концепции и терминология переданы без искажений	5
		имеются немногочисленные неточности в передаче фактического смысла	4
		в тексте есть отдельные искажения смысла	3
		научное содержание текста значительно искажено и не поддаётся восприятию	2

Среднее арифметическое из двух баллов является оценкой за перевод.

При необходимости инвалидам и лицам с ограниченными возможностями здоровья предоставляется дополнительное время для подготовки ответа на зачёте.

При проведении процедуры оценивания результатов обучения инвалидов и лиц с ограниченными возможностями здоровья предусматривается использование технических средств, необходимых им в связи с их индивидуальными особенностями. Эти средства могут быть предоставлены ЧелГУ или могут использоваться собственные технические средства.

Процедура оценивания результатов обучения инвалидов и лиц с ограниченными возможностями здоровья по дисциплине (модулю) предусматривает предоставление информации в формах, адаптированных к ограничениям их здоровья и восприятия

информации:

Для лиц с нарушениями зрения:

– в печатной форме увеличенным шрифтом,

– в форме электронного документа,

Для лиц с нарушениями слуха:

– в печатной форме,

– в форме электронного документа.

Для лиц с нарушениями опорно-двигательного аппарата:

– в печатной форме,

– в форме электронного документа,

Данный перечень может быть конкретизирован в зависимости от контингента обучающихся.

При проведении процедуры оценивания результатов обучения инвалидов и лиц с ограниченными возможностями здоровья по дисциплине обеспечивается выполнение следующих дополнительных требований в зависимости от индивидуальных особенностей обучающихся:

а) инструкция по порядку проведения процедуры оценивания предоставляется в доступной форме (устно, в письменной форме, устно с использованием услуг сурдопереводчика);

б) доступная форма предоставления заданий оценочных средств (в печатной форме, в печатной форме увеличенным шрифтом, в форме электронного документа, задания зачитываются ассистентом, задания предоставляются с использованием сурдоперевода);

в) доступная форма предоставления ответов на задания (письменно на бумаге, набор ответов на компьютере, с использованием услуг ассистента, устно).

При необходимости для обучающихся с ограниченными возможностями здоровья и инвалидов процедура оценивания результатов обучения по дисциплине может проводиться в несколько этапов.

Проведение процедуры оценивания результатов обучения инвалидов и лиц с ограниченными возможностями здоровья допускается с использованием дистанционных образовательных технологий.

4.3 Результаты промежуточной аттестации и уровни сформированности компетенций

«Зачтено» – студент способен структурировано и логично представить итоговое задание, ясно и кратко излагает ответы на уточняющие вопросы; свободно и грамотно излагает свои мысли на английском языке. Допускаются небольшие погрешности и/или неточности в изложении.

«Не зачтено» – итоговое задание, представленное студентом, характеризуется несвязностью и отсутствием какой-либо структуры; студент допускает грубые ошибки грамматического и фактического характера.

Уровни сформированности компетенций определяется следующим образом:

1. Пороговый уровень: предполагает формирование компетенций на начальном уровне – знание английских аналогов основных биологических терминов, обозначений лабораторного оборудования и инструментов.
2. Базовый уровень: предполагает формирование компетенций на более высоком уровне – навыки поиска научной информации медико-биологической направленности в англоязычных источниках.
3. Продвинутый уровень: предполагает формирование компетенций на высоком уровне, готовность к самостоятельной профессиональной деятельности – навык презентации результатов своей научной деятельности на английском языке в рамках международного научной коммуникации.

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Протокол заседания № 6 от 21.02.2025

Председатель Ученого совета
биологического факультета согласовано Д.С. Сташкевич

Заседанием кафедры микробиологии, иммунологии и общей биологии

Протокол заседания № 6 от 21.02.2025

Заведующий кафедрой согласовано А. Л. Бурмистрова
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