12. Antimikrobik Kemoterapi Günleri

Deneysel enfeksiyon modellerinde yeni yaklaşımlar

Doç. Dr. Meral Karaman

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Dokuz Eylül Üniversitesi Tıp Fakültesi, Tıbbi Mikrobiyoloji AD.

Dokuz Eylül Üniversitesi Sağlık Bilimleri Enstitüsü, Laboratuar Hayvanları Bilimi AD.

Süremizin kısıtlı olması nedeniyle;

- In vitro modeller,
- Hayvan modellerinin tarihçesi, etik ilkeler
- Neden sıklıkla kemirgen (sıçan, fare) modelleri,
- *C. elegans, D. melanogaster gibi omurgasız modelleri,*
- Konağa özgü immün yanıtlar, sinyal yolakları,
- …

Bu sunum içinde yer almamaktadır.

Sunum akışı

- Ex vivo enfeksiyon modelleri

- In vivo (Hayvan) enfeksiyon modelleri;

  ✓Güncel rehberler
  ✓Omurgalı-memeli hayvan modellerine yeni bakış
  ✓Omurgalı-memeli olmayan hayvan modelleri
  ✓Omurgasız hayvan modellerinde öne çıkanlar

Ex vivo modeller

3R Russell&Burch

The Principles of Humane Experimental Technique (1959)

- Replacement
- Reduction
- Refinement
- Responsibility

Bill Russell - Rex Burch

http://3rs.ccac.ca/en/about/three-rs.html

Ex vivo modeller

3R Russell&Burch

The Principles of Humane Experimental Technique (1959)

- **Replacement**
- Reduction
- Refinement
- Responsibility

Bill Russell - Rex Burch

http://3rs.ccac.ca/en/about/three-rs.html

Ex vivo modeller

transatlantic think tank for toxicology

t4 Workshop Report*

Non-Animal Models of Epithelial Barriers (Skin, Intestine and Lung) in Research, Industrial Applications and Regulatory Toxicology

Sarah Gordon[1], Mardas Daneshian[2], Joke Bouwstra[3], Francesca Caloni[4], Samuel Constant[5], Donna E. Davies[6,7], Gudrun Dandekar[8], Carlos A. Guzman[9], Eric Fabian[10], Eleonore Haltner[11], Thomas Hartung[2,12], Nina Hasiwa[2], Patrick Hayden[13], Helena Kandarova[14], Sangeeta Khare[15], Harald F. Krug[16], Carsten Kneuer[17], Marcel Leist[2], Guoping Lian[18,19], Uwe Marx[20,21], Marco Metzger[8], Katharina Ott[10], Pilar Prieto[22], Michael S. Roberts[23], Erwin L. Roggen[24], Tewes Tralau[25], Claudia van den Braak[26], Heike Walles[8] and Claus-Michael Lehr[1]

*A report of t4 – the transatlantic think tank for toxicology, a collaboration of the toxicologically oriented chairs in Baltimore, Konstanz and Utrecht sponsored by the Doerenkamp Zbinden Foundation. The views expressed in this article are those of the contributing authors and do not necessarily reflect those of their institution of employment.

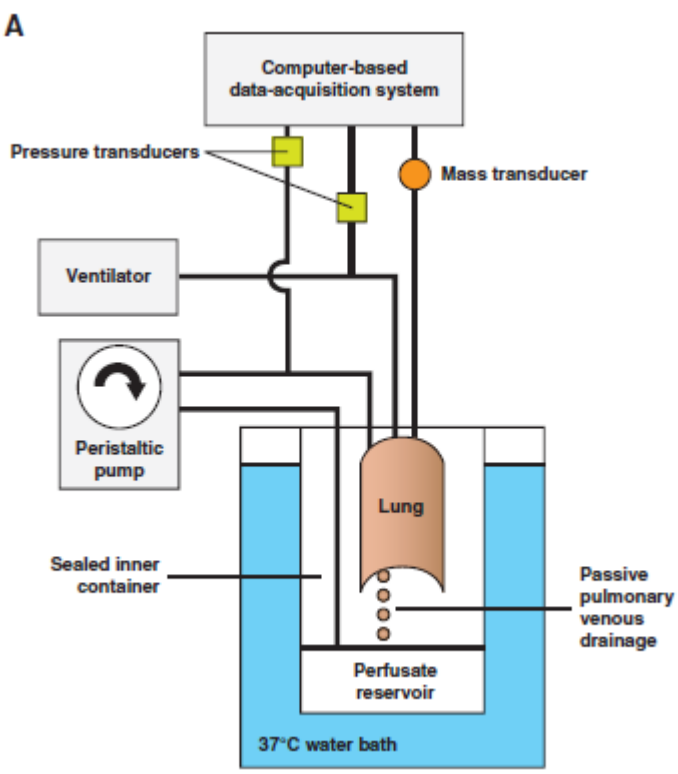
ALTEX 32(4), 2015

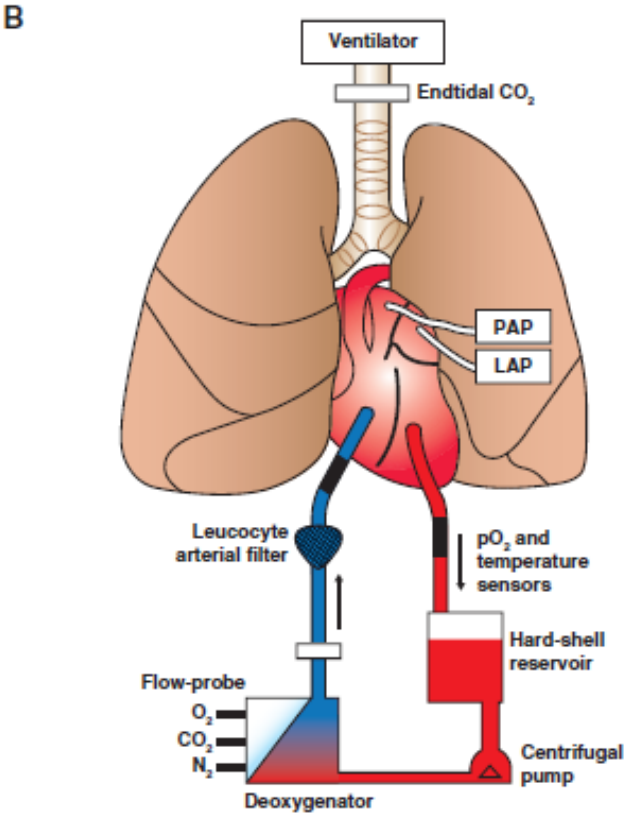
Disease Models & Mechanisms 4, 145-153 (2011) doi:10.1242/dmm.006213

CLINICAL PUZZLE

Human models of acute lung injury

Alastair G. Proudfoot[1], Danny F. McAuley[2,3], Mark J. D. Griffiths[1,4,*] and Matthew Hind[1,4,*,‡]



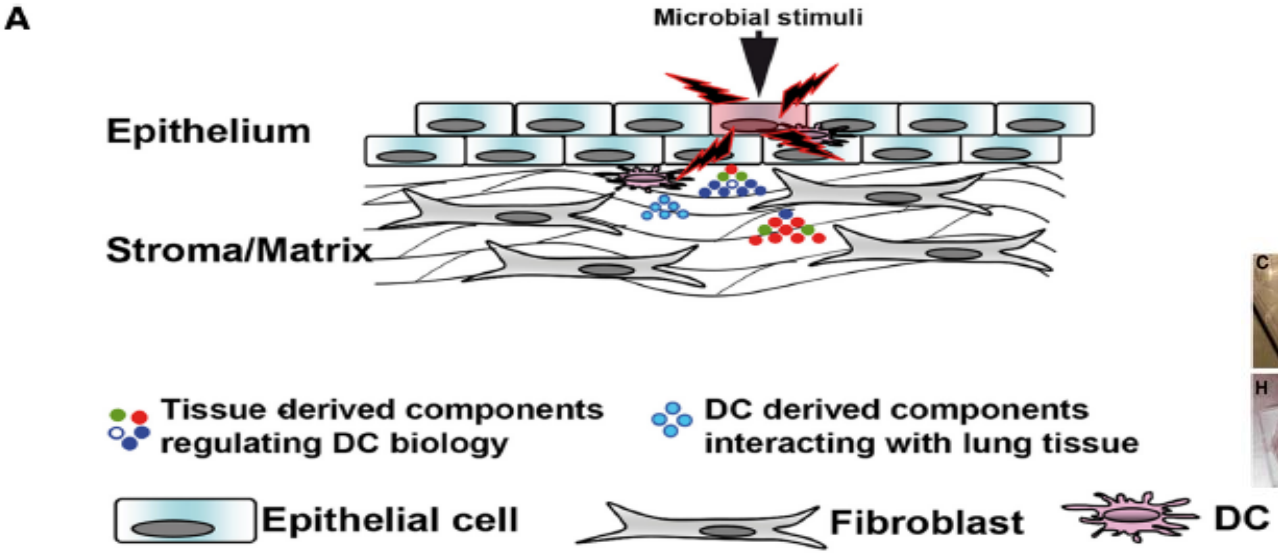


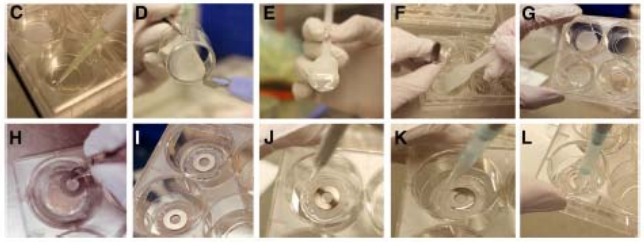
JLB

TECHNICAL ADVANCE

Technical Advance: Live-imaging analysis of human dendritic cell migrating behavior under the influence of immune-stimulating reagents in an organotypic model of lung

Anh Thu Nguyen Hoang,[*,1] Puran Chen,*[*,1] Sofia Björnfot,*[*] Kari Högstrand,*[*,2] John G. Lock,[†] Alf Grandien,*[,2] Mark Coles,[‡] and Mattias Svensson*[*,3]*



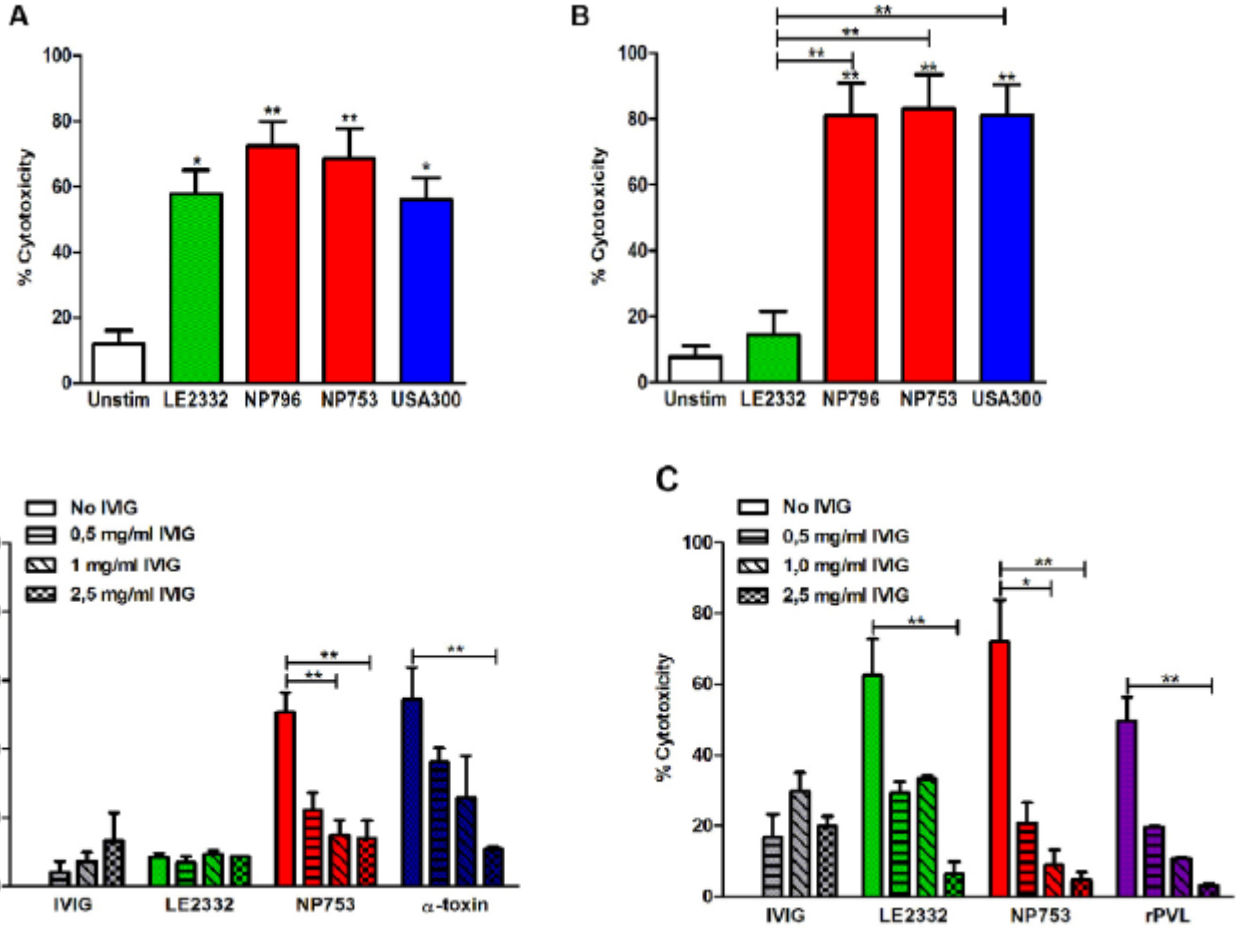


© 2015. Published by The Company of Biologists Ltd | Disease Models & Mechanisms (2015) 8, 1413-1425 doi:10.1242/dmm.021923

RESEARCH ARTICLE

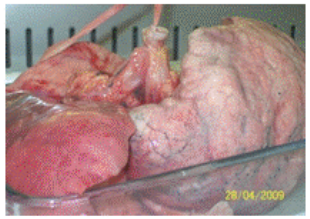
Modelling staphylococcal pneumonia in a human 3D lung tissue model system delineates toxin-mediated pathology

Srikanth Mairpady Shambat[1], Puran Chen[1], Anh Thu Nguyen Hoang[1], Helena Bergsten[1], Francois Vandenesch[2,3], Nikolai Siemens[1], Gerard Lina[2,3], Ian R. Monk[4], Timothy J. Foster[4], Gayathri Arakere[5], Mattias Svensson[1,*] and Anna Norrby-Teglund[1,*,‡]

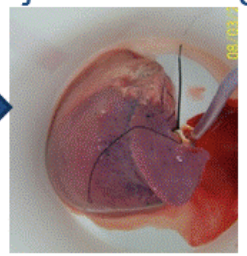


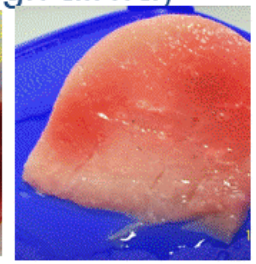
Experience with Precision Cut Lung Slices (PCLS)

Whole diseased organs available

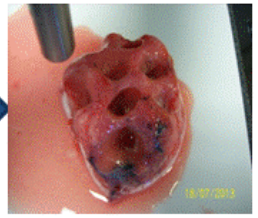


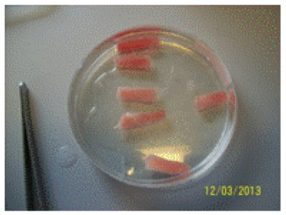
Tissue stabilised with agarose injected through airway





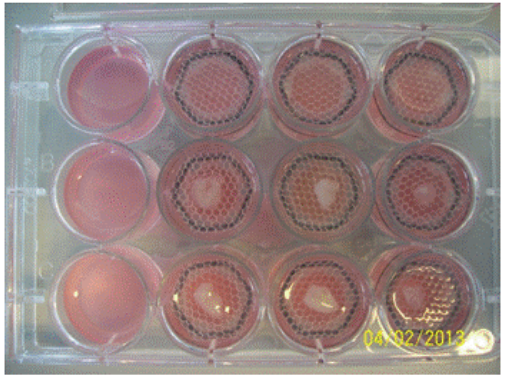
Cores taken through tissue





Slices cut

Slices suspended on a mesh in culture medium



biopta
human tissue experts

Human and animal lung slices

Experimental and Toxicologic Pathology 68 (2016) 77–87

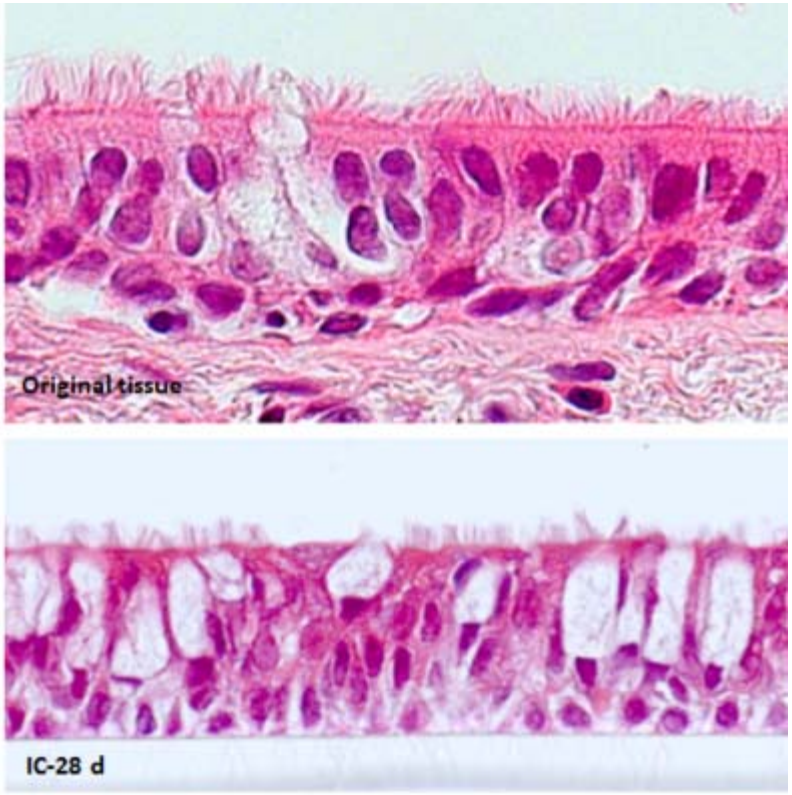
Contents lists available at ScienceDirect

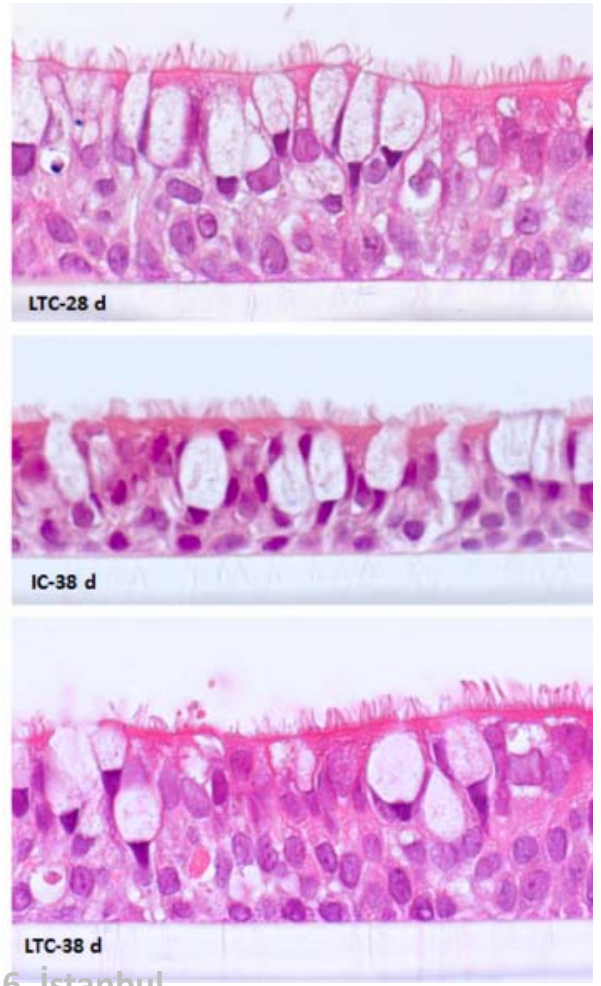
Experimental and Toxicologic Pathology

journal homepage: www.elsevier.de/etp

A new computer-controlled air–liquid interface cultivation system for the generation of differentiated cell cultures of the airway epithelium

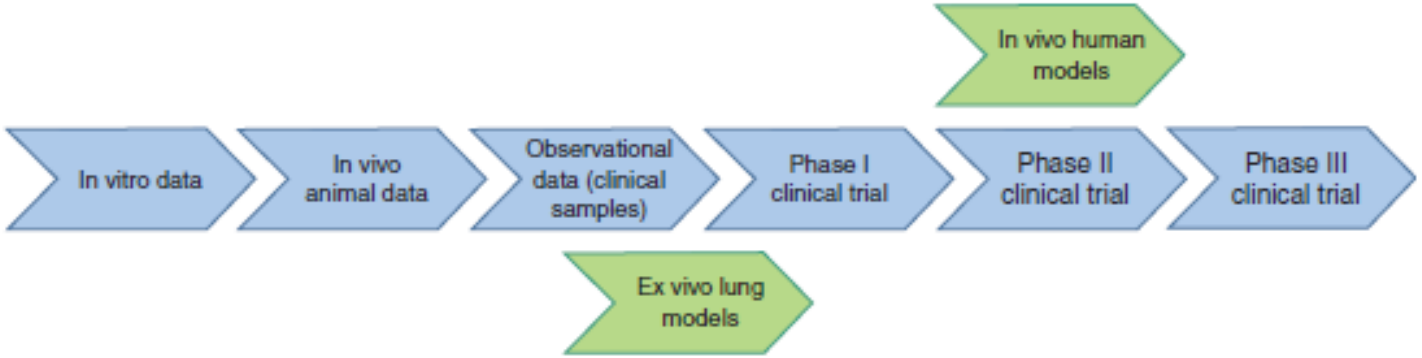
Michaela Aufderheide[a,*], Christine Förster[b], Morris Beschay[c], Detlev Branscheid[c], Makito Emura[a]





Ex vivo modeller

Üstünlükleri	Kısıtlılıkları
Etik kaygıların azlığı	Pahalı, ileri teknik donanım
Sınırsız örnekleme	Az sayıda merkez ve deneyimli kişi
Uzun süre canlılığını koruma	Vericiye ilişkin öykü?
Standart koşullar	Sistem değerlendirmesi?



Omurgalı-memeli hayvan modellerine yeni bakış

Hayvan deneyleri için güncel rehberler

- Russell &Burch (1959); The Principles of Humane Experimental Techniques
- The Federation of European Laboratory Animal Science Associations (FELASA) (1978); Guidelines and Recommendations
- ARRIVE (Animals in Research: Reporting In Vivo Experiments); 2010
- Mouse Grimace Scale (MGS)(Langford 2010); Coding of facial expressions of pain in the laboratory mouse
- FRAME

www.felasa.eu

felasa

Federation of European Laboratory Animal Science Associations

WORKING PARTY REPORT

 Laboratory Animals (2002) 36, 20–42

Recommendations for the health monitoring of rodent and rabbit colonies in breeding and experimental units

Recommendations of the Federation of European Laboratory Animal Science Associations (FELASA) Working Group on Health Monitoring of Rodent and Rabbit Colonies accepted by the FELASA Board of Management, 9 June 2001

FELASA Working Group on Health Monitoring of Rodent and Rabbit Colonies: W. Nicklas (Convenor), P. Baneux, R. Boot, T. Decelle, A. A. Deeny, M. Fumanelli & B. Illgen-Wilcke

FELASA, BCM Box 2989, London WC1N 3XX, UK

BJP BRITISH JOURNAL OF PHARMACOLOGY

BPS BRITISH PHARMACOLOGICAL SOCIETY

BJP British Journal of Pharmacology

DOI:10.1111/j.1476-5381.2010.00872.x
www.brjpharmacol.org

GUIDELINES

Animal research: Reporting *in vivo* experiments: The ARRIVE guidelines

Carol Kilkenny[1†], William Browne[2], Innes C Cuthil
and Douglas G Altman[5]

[1]*The National Centre for the Replacement, Refinement and Reductio London, UK,* [2]*Department of Clinical Veterinary Science, University Biological Sciences, University of Bristol, Bristol, UK,* [4]*National Hea Imperial College London, UK and* [5]*Centre for Statistics in Medicine, Oxford, UK*

[†]Corresponding author. E-mail:
carol.kilkenny@nc3rs.org.uk

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	

	Item	Recommendation (Kilkenny *et al.*, 2010)
TITLE	1	Provide as accurate and concise a description of the content of the article as possible.
ABSTRACT	2	Provide an accurate summary of the background, research objectives, including details of the species or strain of animal used, key methods, principal findings and conclusions of the study.
INTRODUCTION		
Background	3	a. Include sufficient scientific background (including relevant references to previous work) to understand the motivation and context for the study, and explain the experimental approach and rationale. b. Explain how and why the animal species and model being used can address the scientific objectives and, where appropriate, the study's relevance to human biology.
Objectives	4	Clearly describe the primary and any secondary objectives of the study, or specific hypotheses being tested.
Study design	6	For each experiment, give brief details of the study design including: a. The number of experimental and control groups. b. Any steps taken to minimise the effects of subjective bias when allocating animals to treatment (e.g. randomisation procedure) and when assessing results (e.g. if done, describe who was blinded and when). c. The experimental unit (e.g. a single animal, group or cage of animals). A time-line diagram or flow chart can be useful to illustrate how complex study designs were carried out.
Experimental procedures	7	For each experiment and each experimental group, including controls, provide precise details of all procedures carried out. For example: a. How (e.g. drug formulation and dose, site and route of administration, anaesthesia and analgesia used [including monitoring], surgical procedure, method of euthanasia). Provide details of any specialist equipment used, including supplier(s). b. When (e.g. time of day). c. Where (e.g. home cage, laboratory, water maze). d. Why (e.g. rationale for choice of specific anaesthetic, route of administration, drug dose used).

	Item	Recommendation (Kilkenny *et al.*, 2010)
Experimental animals	8	a. Provide details of the animals used, including species, strain, sex, developmental stage (e.g. mean or median age plus age range) and weight (e.g. mean or median weight plus weight range). b. Provide further relevant information such as the source of animals, international strain nomenclature, genetic modification status (e.g. knock-out or transgenic), genotype, health/immune status, drug or test naïve, previous procedures, etc.
Housing and husbandry	9	Provide details of: a. Housing (type of facility e.g. specific pathogen free [SPF]; type of cage or housing; bedding material; number of cage companions; tank shape and material etc. for fish). b. Husbandry conditions (e.g. breeding programme, light/dark cycle, temperature, quality of water etc for fish, type of food, access to food and water, environmental enrichment). c. Welfare-related assessments and interventions that were carried out prior to, during, or after the experiment.
Sample size	10	a. Specify the total number of animals used in each experiment, and the number of animals in each experimental group. b. Explain how the number of animals was arrived at. Provide details of any sample size calculation used. c. Indicate the number of independent replications of each experiment, if relevant.
Allocating animals to experimental groups	11	a. Give full details of how animals were allocated to experimental groups, including randomisation or matching if done. b. Describe the order in which the animals in the different experimental groups were treated and assessed.
		weight, microbiological status, and drug or test naïve) prior to treatment or testing. (This information can often be tabulated).
Numbers analysed	15	a. Report the number of animals in each group included in each analysis. Report absolute numbers (e.g. 10/20, not 50%) (Schulz *et al.*, 2010). b. If any animals or data were not included in the analysis, explain why.
Outcomes and estimation	16	Report the results for each analysis carried out, with a measure of precision (e.g. standard error or confidence interval).
Adverse events	17	a. Give details of all important adverse events in each experimental group. b. Describe any modifications to the experimental protocols made to reduce adverse events.
DISCUSSION		
Interpretation/scientific implications	18	a. Interpret the results, taking into account the study objectives and hypotheses, current theory and other relevant studies in the literature. b. Comment on the study limitations including any potential sources of bias, any limitations of the animal model, and the imprecision associated with the results (Schulz *et al.*, 2010). c. Describe any implications of your experimental methods or findings for the replacement, refinement or reduction (the 3Rs) of the use of animals in research.
Generalisability/ translation	19	Comment on whether, and how, the findings of this study are likely to translate to other species or systems, including any relevance to human biology.
Funding	20	List all funding sources (including grant number) and the role of the funder(s) in the study.

Sample size 10 a. Specify the total number of animals used in each experiment, and the number of animals in each experimental group.
b. Explain how the number of animals was arrived at. Provide details of any sample size calculation used.
c. Indicate the number of independent replications of each experiment, if relevant.

MOUSE GRIMACE SCALE (MGS)

Coding of facial expressions of pain in the laboratory mouse

Dale J Langford[1], Andrea L Bailey[1], Mona Lisa Chanda[1], Sarah E Clarke[1], Tanya E Drummond[1], Stephanie Echols[2], Sarah Glick[1], Joelle Ingrao[1], Tammy Klassen-Ross[2], Michael L LaCroix-Fralish[1], Lynn Matsumiya[1], Robert E Sorge[1], Susana G Sotocinal[1], John M Tabaka[1], David Wong[2], Arn M J M van den Maagdenberg[3,4], Michel D Ferrari[4], Kenneth D Craig[2] & Jeffrey S Mogil[1]

NATURE METHODS | VOL.7 NO.6 | JUNE 2010 | 447

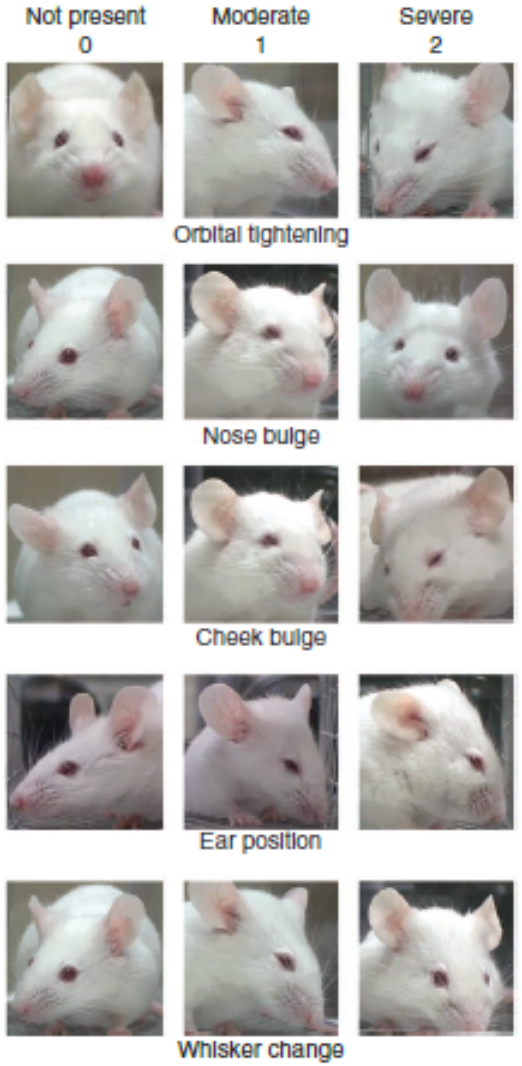
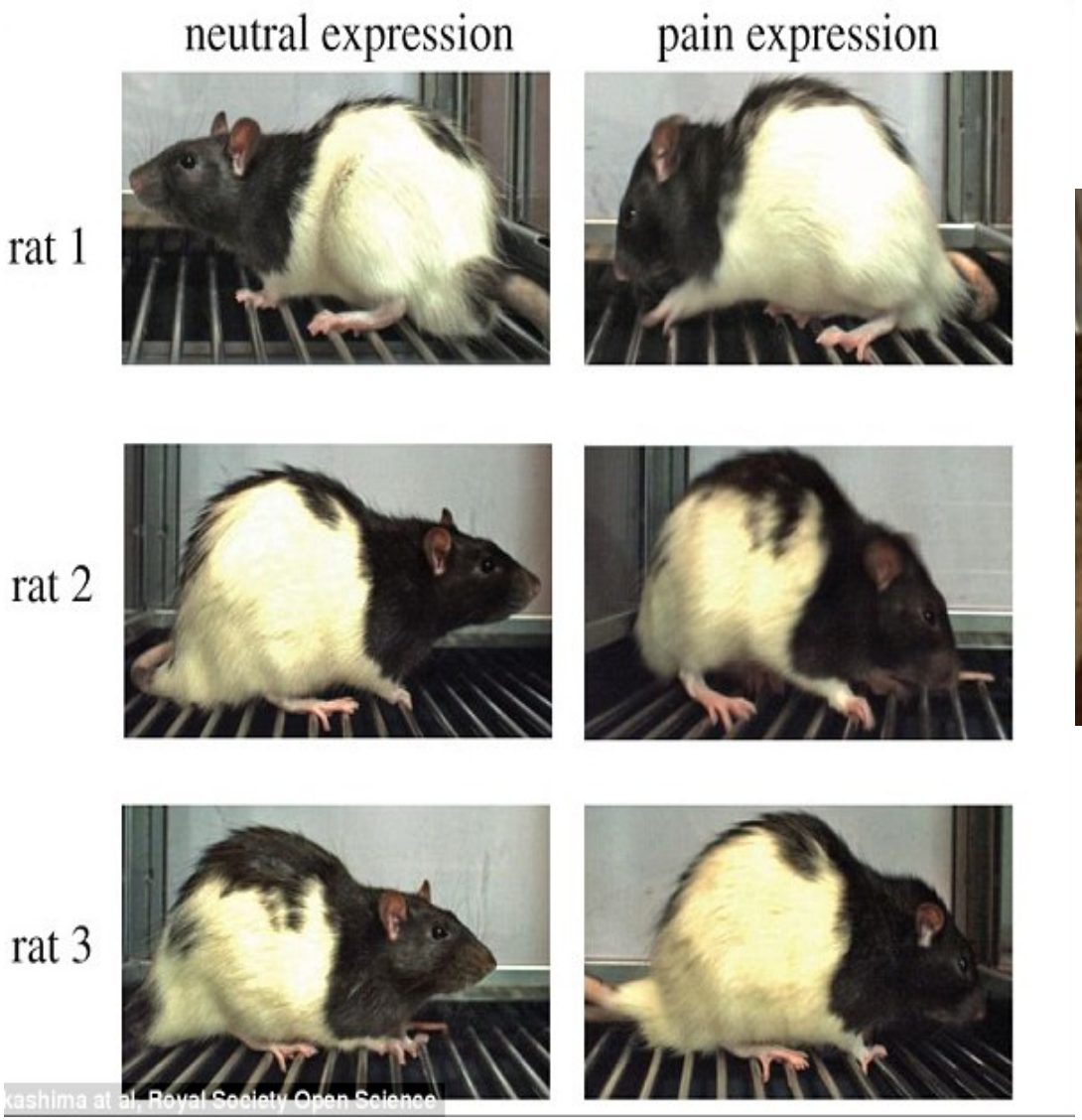


Figure 1 | In the MGS, intensity of each feature is coded on a three-point scale. For each of the five features, images of mice exhibiting behavior corresponding to the three values are shown.

Klinik değerlendirme



Kronik akciğer enfeksiyonu modeli 2. gün

The FRAME Reduction Committee

Was established in 1998 and has now developed into the FRAME Reduction Steering Committee (FRSC) overseeing a number of working parties.

Members of the committee are representatives from industry, the Home Office, and academia, with expertise in statistics, experimental design, animal welfare and alternatives research.

The Committee's main aim is:

'To reduce the number of animals used in research, education and testing without compromising the quality of research or hindering scientific progress'

FRAME

Believes that the current scale of animal experimentation is unacceptable, but recognises that the immediate abolition of all laboratory animal use is not possible.

FRAME advocates the Three Rs (Replacement, Reduction and Refinement) approach to this problem.

It relies entirely on grants and donations to carry out its vital work because it receives no financial support from local or central government. Any gifts from supporters, either individuals or companies, are always welcome.

FRAME
Russell & Burch House
96-98 North Sherwood St.
Nottingham,
NG1 4EE, UK.

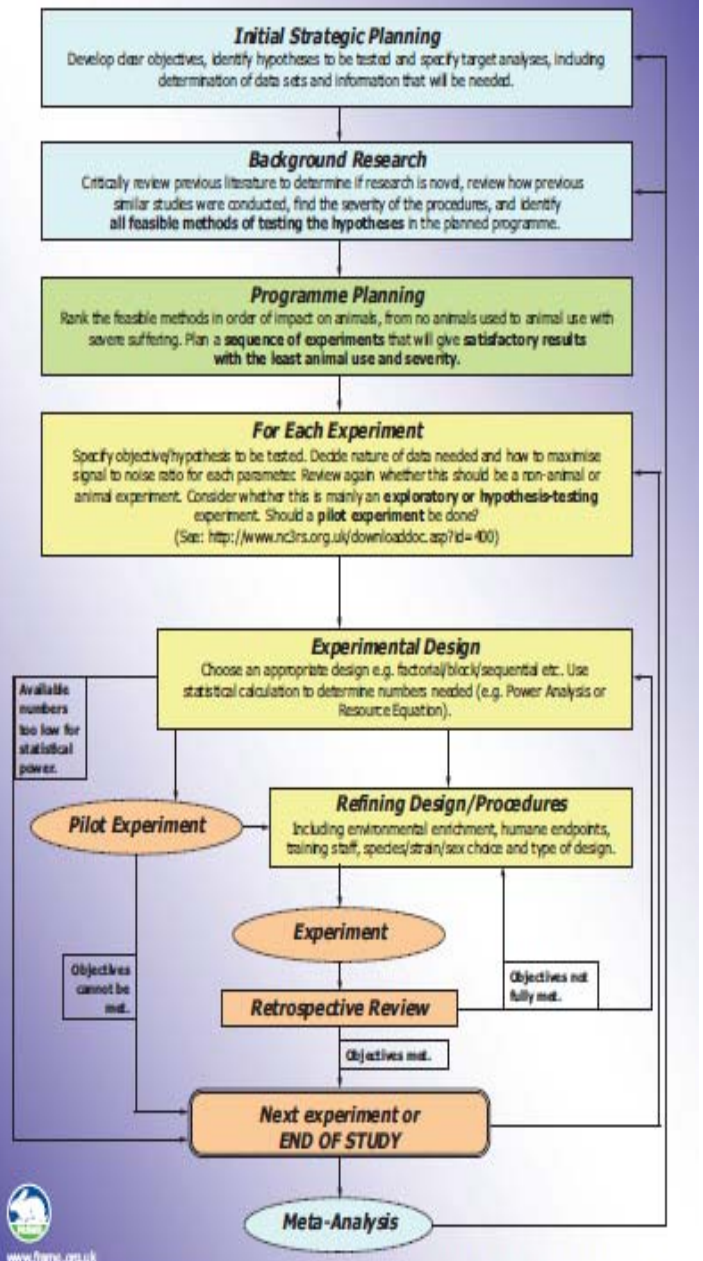
FRAME

FRAME Reduction Steering Committee

Strategic Planning Chart For Reducing Animal Use in Biomedical Science

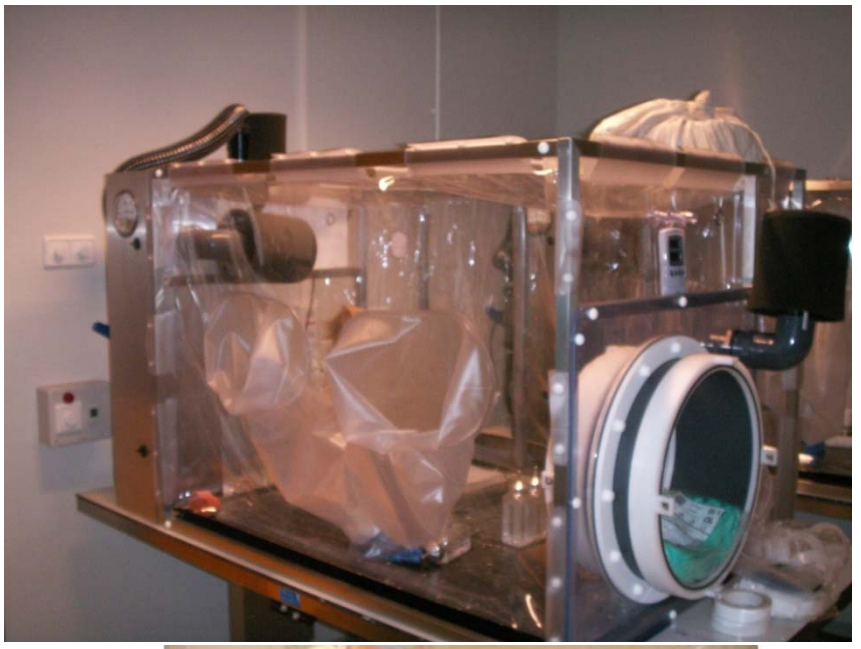
Registered Charity No. 251464

Strategic Planning for Research Programmes



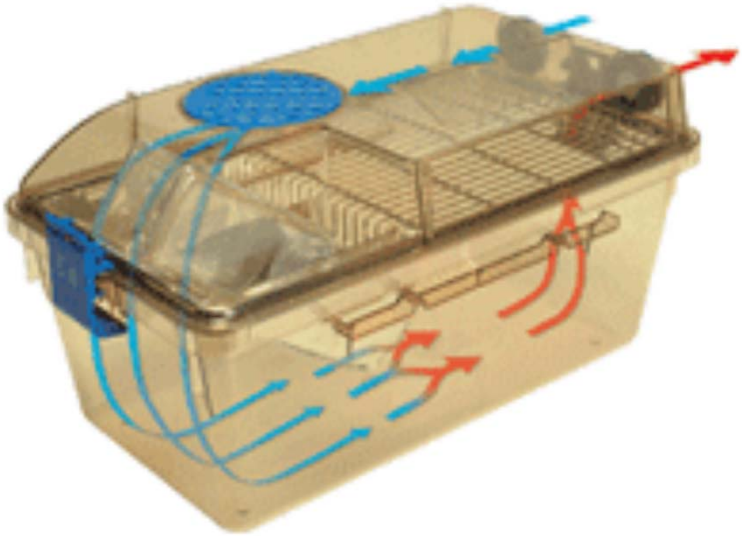
http://www.frame.org.uk

Laboratuar hayvanı yetiştiriciliği ve enfeksiyon modelerinde teknolojik gelişmeler



Biyobalon bariyer sistemleri

IVC (Individual Ventilated Cages)



http://www.tecniplast.it/en/product/green-line-ivc-sealsafe-plus-rat.html

ABSL-3 ISOCAGE

- Yüksek biyogüvenlik
- Negatif basınç altında (-100 pa)

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RESEARCH ARTICLE

Increased susceptibility to otitis media in a *Splunc1*-deficient mouse model

Jennifer A. Bartlett[1,*], David K. Meyerholz[2,*], Christine L. Wohlford-Lenane[1], Paul W. Naumann[2], Nita H. Salzman[3] and Paul B. McCray, Jr[1,‡]

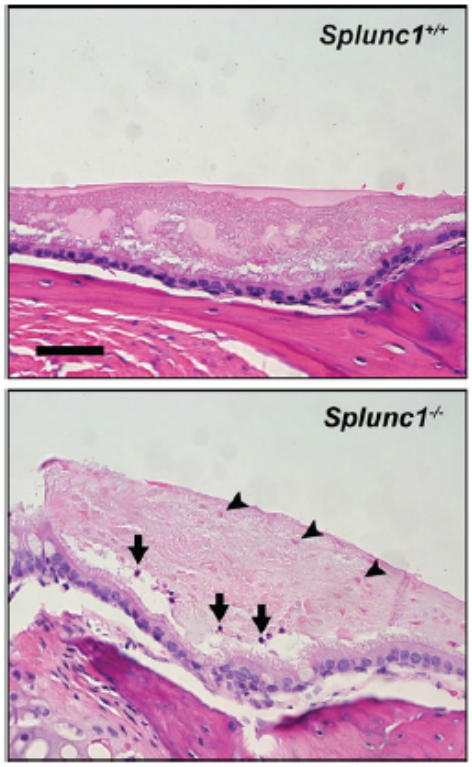


Fig. 4. The middle ears of *Splunc1*$^{-/-}$ mice harbor increased inflammatory cells and cellular debris relative to wild-type littermate controls. The top panel depicts a representative image of a middle ear from a *Splunc1*$^{+/+}$ mouse, in which the middle ear epithelium is covered by a layer of fluid containing globular fluid material. In the *Splunc1*$^{-/-}$ middle ear image (bottom panel) this fluid contains multiple punctate eosinophilic 'ghost' cells (black arrowheads) along with a small number of solitary PMNs (black arrows). Scale bar: 43 µm.

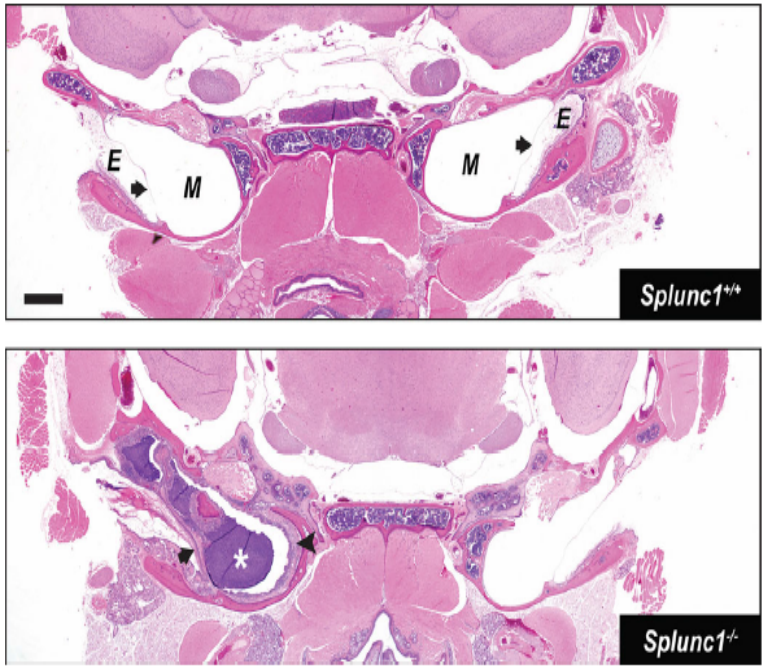


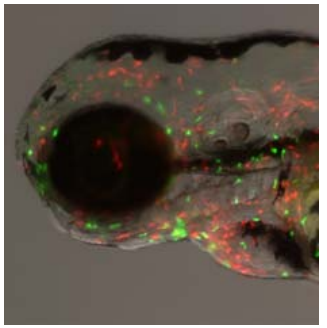
Fig. 2. Unilateral otitis media in a *Splunc1*$^{-/-}$ mouse. H&E-stained coronal sections through the heads of 10- to 18-month-old *Splunc1*$^{+/+}$ and *Splunc1*$^{-/-}$ mice were inspected for gross abnormalities. The top panel depicts a representative coronal section from a *Splunc1*$^{+/+}$ mouse. The bottom panel is from a *Splunc1*$^{-/-}$ mouse exhibiting unilateral otitis media, characterized by purulent material in the middle ear lumen (white asterisk). In this mouse, thickening of the tympanic membrane and middle ear epithelium (black arrowhead) are indicative of chronic otitis media. E, external ear canal; M, middle ear; in both panels, black arrows indicate the tympanic membranes. Scale bar: 0.7 mm.

Omurgalı-memeli olmayan hayvan modelleri
Zebra balığı (*Danio rerio*)

- Embriyo gelişimindeki genetik kontrolünün kolaylığı ve deneysel avantajlarından dolayı en sık kullanılan model organizma,
- Üretimi kolay, gelişimi hızlı (Embriyogenez-24 saat, organ oluşumu-5 gün)
- Mikroenjeksiyon ve hücre transplantasyonu gibi deneysel manipülasyonlara karşı dayanıklıdır
- Laboratuvar koşulları altında yıl boyunca yumurtlayabilir (200 yumurta/hafta)

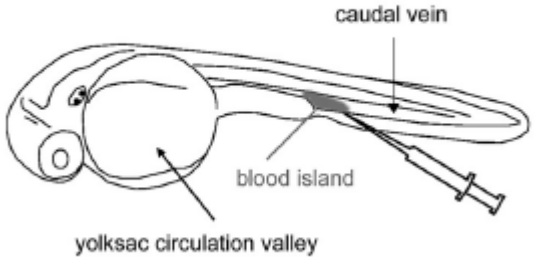
Omurgalı-memeli olmayan hayvan modelleri
Zebra balığı (Danio rerio)

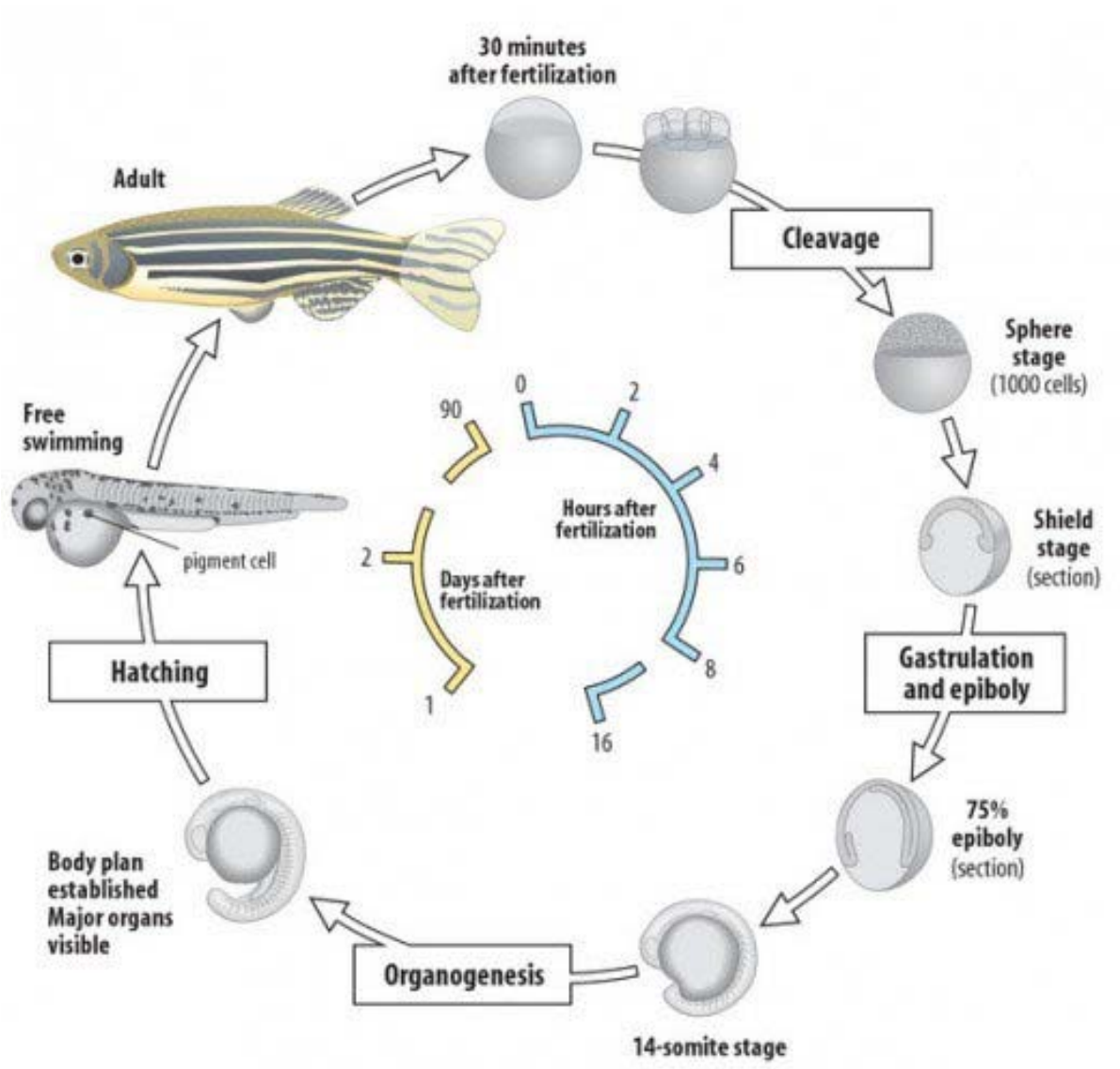
- Koriyon ve embriyosu saydam (florosan ile işaretlenmiş transgenlerin ekspresyonu, gen aktivitesi, patojenin inokulasyonundan sonra enfeksiyonun eş zamanlı izlemi)



- Memeli immün sistemi ile benzerlikleri (Kazanılmış immün sistem fertilizasyondan sonra 4. haftaya kadar fonksiyonel değil, doğal immün sistemi ise memelilere benzer, genç embriyolarda da var)

Zebra balığı gelişim evreleri



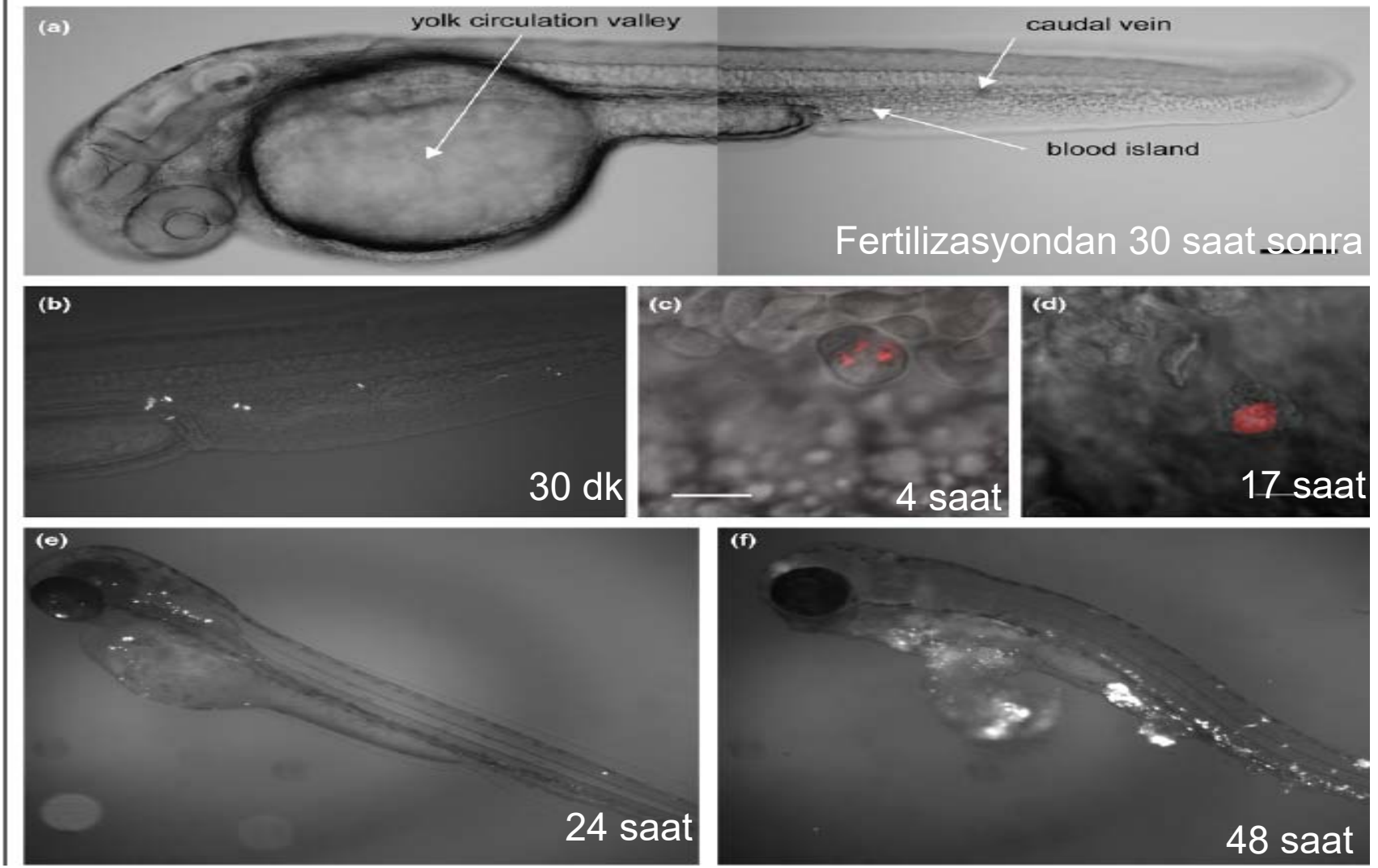


http://hubpages.com/animals/The-why-and-how-of-breeding-zebrafish-for-research

INFECTION AND IMMUNITY, Apr. 2010, p. 1495–1508 Vol. 78, No. 4
0019-9567/10/$12.00 doi:10.1128/IAI.00743-09

Burkholderia cenocepacia Creates an Intramacrophage Replication Niche in Zebrafish Embryos, Followed by Bacterial Dissemination and Establishment of Systemic Infection▽†

Annette C. Vergunst,[1,2]* Annemarie H. Meijer,[3] Stephen A. Renshaw,[4] and David O'Callaghan[1,2]

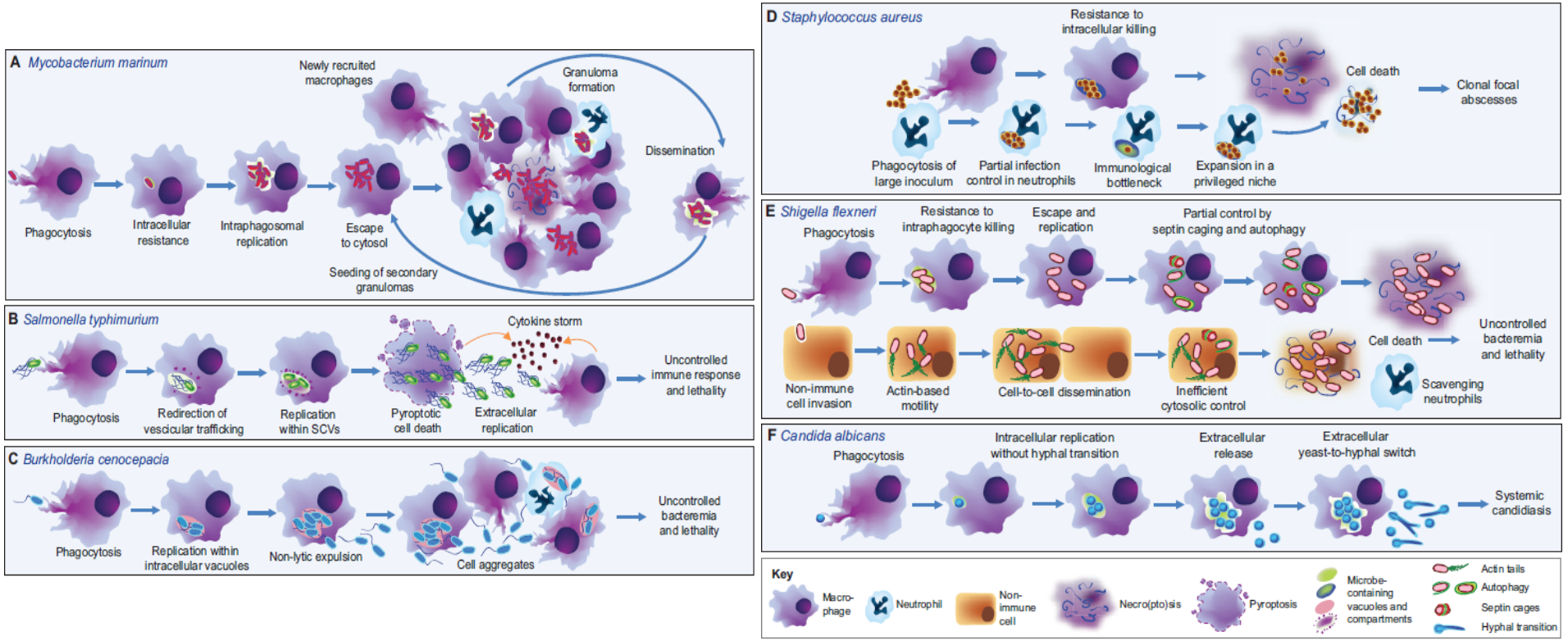


© 2014. Published by The Company of Biologists Ltd | Disease Models & Mechanisms (2014) 7, 785-797 doi:10.1242/dmm.015594

REVIEW

Macrophage-pathogen interactions in infectious diseases: new therapeutic insights from the zebrafish host model

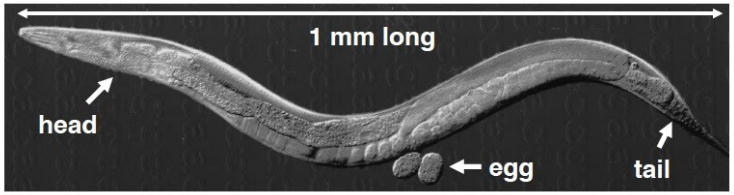
Vincenzo Torraca, Samrah Masud, Herman P. Spaink and Annemarie H. Meijer*



Omurgasız hayvan modellerinde öne çıkanlar

- *Drosophila melanogaster,*

- *Caenorhabditis elegans,*



C. elegans **hermaphrodite adult**

- *Bombyx mori*

- *Galleria mellonella*

Omurgasız hayvan modellerinde öne çıkanlar

- *Drosophila melanogaster,*
- *Caenorhabditis elegans,*
- *Bombyx mori*
- ***Galleria mellonella***

G. mellonella (Lepidoptera: Pyralidae) gelişim evreleri

The Development of the Greater Wax Moth

-night active moth
-wing-span 14-38 mm
-does not feed
-survival 1-3 weeks [5]
-female lays 300-1000 eggs [3;4]

-duration of cycle under ideal conditions; About 6 weeks
-4-6 generations per year [3]

Duration: 1-9 weeks [5]

Imago

Pupa

Eggs

Larva

-in cocoon
-immobile phase
-does not feed

-cluter or 50-150 eggs [4]
-olive shaped, 1/2 mm
-white—reddish

Temp. °C	Duration (days) [5]
24-27°	5-8
10-16°	>35
> 9°	Development stopped

-very active stage → Damage
-grows from 1 to >23 mm
-8-10 stages (skin shedding)
-last stage spins cocoon
-duration: 28 days—6 months depending on temperature and food [5]
-ideal temperature: 29-35° C [5]
-development stops at <15° C [6]

Galleria mellonella (Lepidoptera: Pyralidae)
(The greater wax moth; Büyük balmumu güvesi)

- Etik açıdan daha az endişe
- Düşük maliyet
- Kolay uygulama
- Çok çeşitli alanlarda kullanabilme
- Sistemik olarak patojenlerin ya da antimikrobiyal ilaçların uygulanabilmesi
- Koruyucu ya da tedavi edici etkinliklerin test edilebilmesi
- Çok sayıda uygulamaya izin vermesi
- Deneyin çok sayıda tekrar edilebilmesi
- ~20-50 µL hemolenf eldesi
- 15-37°C'da yaşayabilme

Memeli modelleri ile uyumlu sonuçlar

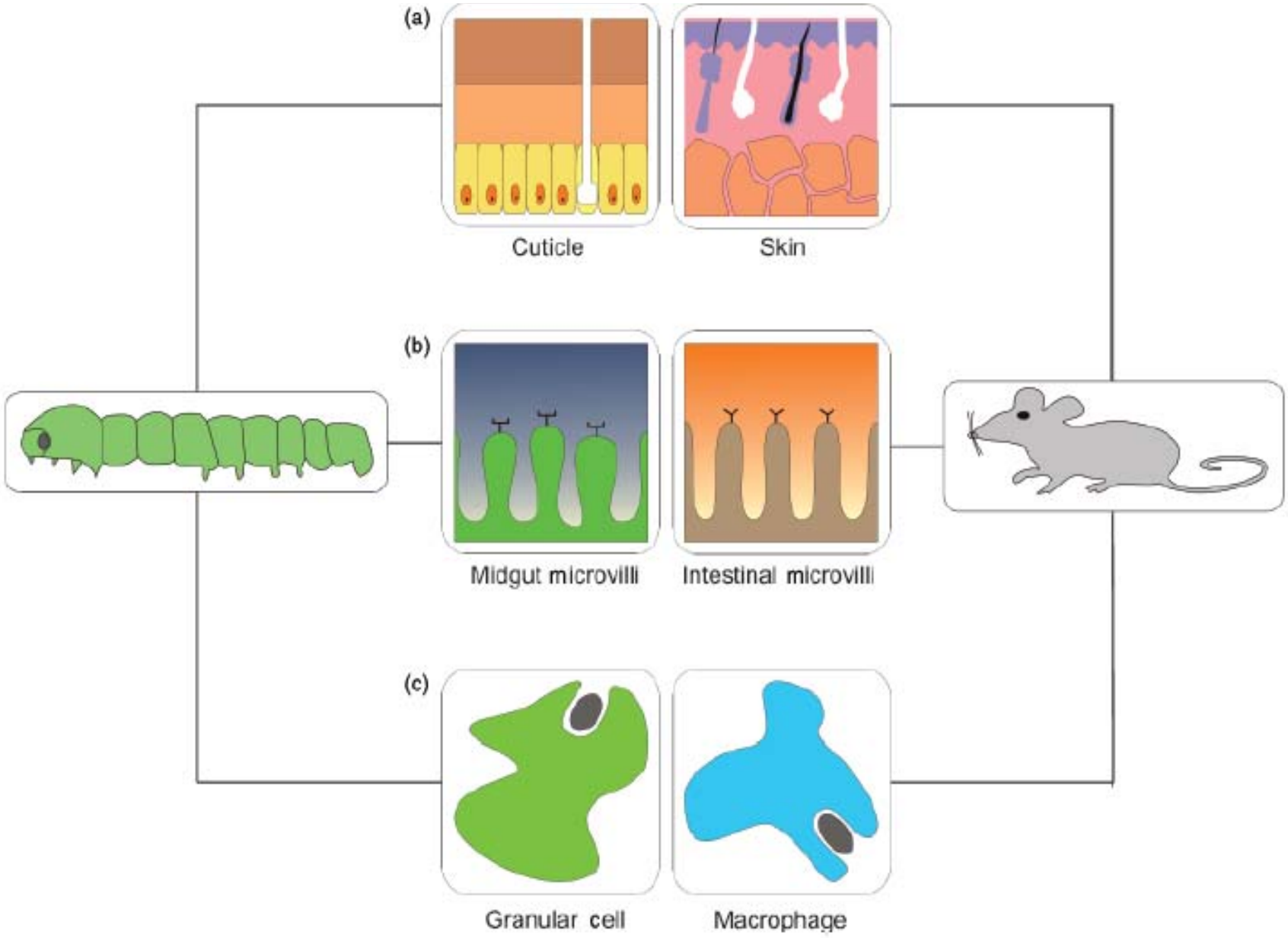
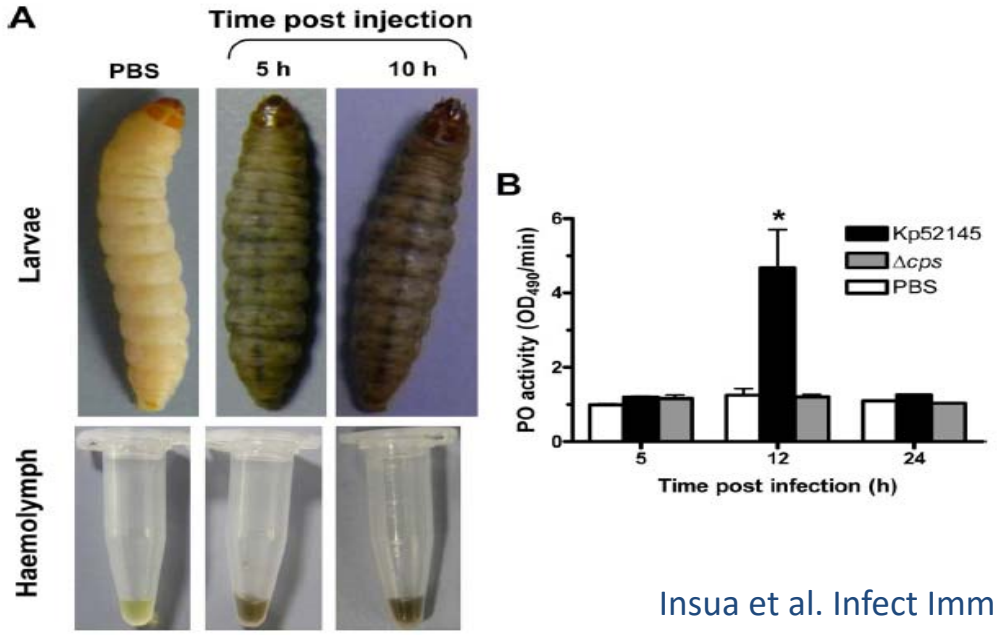


Fig. 1. Parallels between mammals and insects with respect to microbial infection. (a) During infection, pathogens secrete proteases to degrade the protein component of insect cuticle or compromised mammalian epidermis. (b) Toxins exert their effect by binding to receptors on the intestinal microvilli of mammals or the insect midgut. (c) Foreign invaders are engulfed by granular cells that patrol the insect hemolymph or macrophages circulating in the mammalian blood stream.

Schully et al. FEMS Microbiol Lett ,2006; 263: 1–9.

Humoral immün yanıt

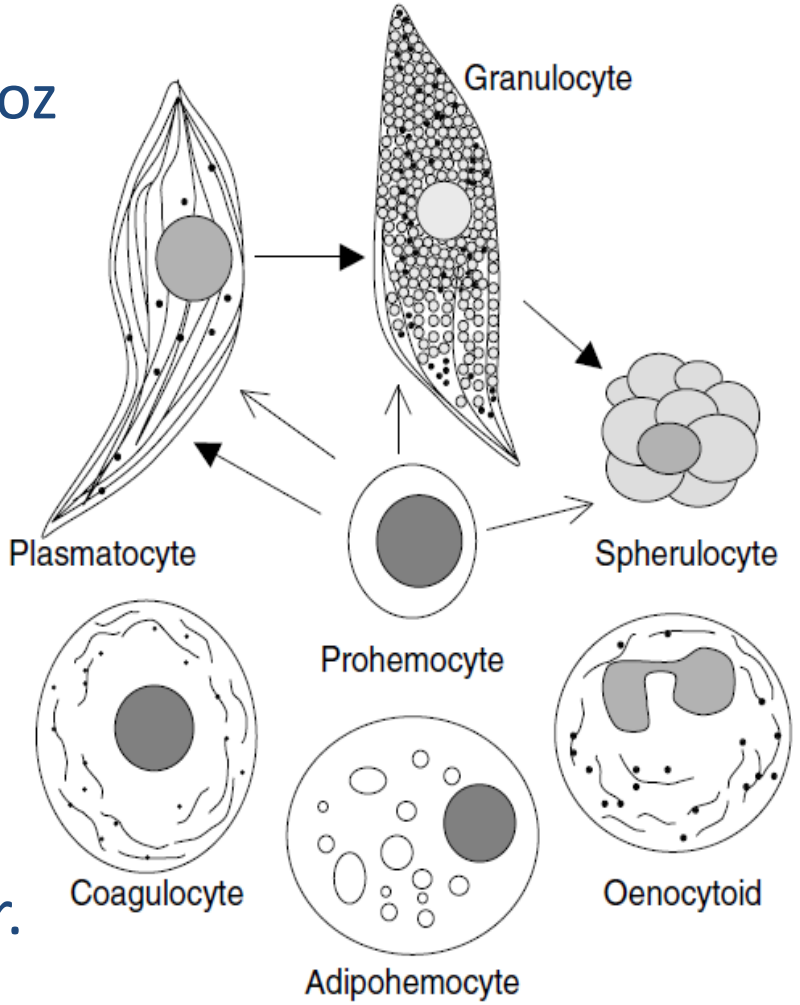
- Kütikül hasarı humoral immün yanıtı uyarır.
- Melanizasyon; profenoloksidaz (PPO) hemositlerde sentezlenir. Kütikülde aktif formuna dönüşür.
- Hemolenf pıhtılaşması; fenoloksidaz ve Ca^{+2} bağımlı transglutaminaz etkisi
- Antimikrobiyal peptid ve Hsp sentezi



Insua et al. Infect Immun 2013;81(10): 3552–65

Hemolenf-Kan

- Hemolenf, memelilerdeki fagositoz etkinliğine benzer fonksiyonları olan “hemositleri” içerir.
- *G. mellonella’*da en az 6 farklı hemosit olduğu bildirilmektedir.
- Hemosit dansitesi ve hemosit tipleri enfeksiyöz etkenlere bağlı olarak farklılıklar göstermektedir.



Kavanagh et al. FEMS Microbiol Rev,2004;2:101-12

Hücresel immün yanıt

- Fagositoz; Plazmatositler ve granülositler tarafından yürütülen memelilerdekine benzer bir süreçtir.

- Enkapsülasyon ; hemositler tarafından fagosite edilemeyecek kadar büyük olan partiküller için gerçekleştirilir. Patojenin etrafında hemositler yoğun tabaka oluşturur. Kısmi veya tam melanizasyon gerçekleşir.

- Nodül oluşumu; Nodüller patojenin etrafında bulunan, genellikle melanize olmuş nekrotik bir merkeze sahip olan hücre dışı pıhtı ve hemosit agregatlarıdır.

A comparison of humoral and cellular PPRs, and anti-microbial peptides and enzymes in humans and insects

	Vertebrates	Invertebrates
Humoral PRRs	Macrophage mannose receptor (175 kDa). f-Met–Leu–Phe receptor (binds to *N*-formyl peptide).	LPS binding protein
	c-type lectins	Lectins
	C2-type immunoglobulin domain	Hemolin
		β-1,3 glucan binding protein
		Gram (−ve) bacterial recognition protein
		Peptidoglycan recognition protein
	Complement/α2 macroglobulin	αTEPI
	von Willebrand platelet aggregation factor	Hemocytin
	Scavenger receptor	
Cellular PRRs	Toll-like receptors	*Toll*
		Toll 3–8
		18-wheeler
		Immune deficiency (imd)
	Integrins (CD11b/(CD18) and LFA-1.	Integrins (α, β)
		heterodimeric proteins
Cationic proteins	Elastase (29–31 kDa) AB, AF	Attractin/
	Cathepsin G (25–29 kDa) AB, AF	Sarcotoxin (20–28 kDa) AB
	BPI (55–60 kDa) AB	
	Lactoferrin (78 kDa) AB	
	Proteinase 3	
	Azurocidine (29 kDa) AB, AF	
	Lysozyme (14.4 kDa) AB, AF	Lysozyme AB, AF
	MPO/H_2O_2(150 kDa) AB, AF	
Metalloproteinases	Collagenase	Metalloproteinase (297, 198 and 95 kDa)
	Gelatinase	
Peptides	Defensins (4 kDa) AB, AF	Defensins AB
		Cepropins (4 kDa) AF
		Diptericins (9 kDa) AB
		Drosocin AB
		Metchnikowin AB, AF
		Proline-rich anti-microbial peptides AB
		Drosomycin AF
		AFP AF

Anti-bacterial activity (AB) and anti-fungal activity (AF).

Kavanagh et al. FEMS Microbiol Rev,2004;2:101-12

İnsan nötrofilleri ve böcek hemositleri arasındaki benzerlikler

	Hemocytes	Neutrophils
Phagocytosis	Lectin-mediated	Lectin-mediated
ROS	O_2^-, H_2O_2, NO^-	O_2^-, H_2O_2, NO^-
Degranulation	Yes	Yes
AMPs	Peroxynectin, transferrin, lysozyme, defensin	MPO, transferrin, lysozyme, defensin
Receptors	TLRs, B-1,3-glucan, IL-IR	TLRs, B-1,3-glucan, IL-IR
Transcription factors	NFκB, IκB	NFκB, IκB
Cascades	IMD, JNK, JAK-STAT	IMD, JNK, JAK-STAT
Kinases	p38 MAPK, ERK, PKC, PKA	p38 MAPK, ERK, PKC, PKA
Neutrophil extracellular nets (NET)	NET-like structures present	NETs present

Browne et al. Virulence 2013; 4(7):597-603

G. mellonella gelişim evreleri ve yetiştirme ortamı*

Son larva evresi

Pupa

Kelebek

Yetiştirme ortamı

*Fotoğraflar çalışmalarımızdan alınmıştır.

JOURNAL OF BACTERIOLOGY, July 2000, p. 3843–3845 Vol. 182, No. 13
0021-9193/00/$04.00+0

Positive Correlation between Virulence of *Pseudomonas aeruginosa* Mutants in Mice and Insects

GEORG JANDER,[1]† LAURENCE G. RAHME,[2] AND FREDERICK M. AUSUBEL[1]*

ELSEVIER

FEMS Immunology and Medical Microbiology 34 (2002) 153–157

FEMS
Immunology and
Medical Microbiology

www.fems-microbiology.org

Correlation between virulence of *Candida albicans* mutants in mice and *Galleria mellonella* larvae

Marc Brennan [a], David Y. Thomas [b–d,1], Malcolm Whiteway [b,c], Kevin Kavanagh [a,*]

Virulence 2:2, 111-119; March/April 2011; © 2011 Landes Bioscience

Virulence of serotype M3 Group A Streptococcus strains in wax worms (*Galleria mellonella* larvae)

Randall J. Olsen,* M. Ebru Watkins, Concepcion C. Cantu, Stephen B. Beres and James M. Musser

Virulence 4:4, 324–332; May 15, 2013; © 2013 Landes Bioscience

Brain infection and activation of neuronal repair mechanisms by the human pathogen *Listeria monocytogenes* in the lepidopteran model host *Galleria mellonella*

Krishnendu Mukherjee,[1] Torsten Hain,[2] Rainer Fischer,[3] Trinad Chakraborty[2,*] and Andreas Vilcinskas[1,*]

Giannouli et al. BMC Microbiology 2014, 14:228
http://www.biomedcentral.com/1471-2180/14/228

BMC Microbiology

METHODOLOGY ARTICLE Open Access

Use of larvae of the wax moth *Galleria mellonella* as an in vivo model to study the virulence of *Helicobacter pylori*

Maria Giannouli[1,2], Anna Teresa Palatucci[3,4], Valentina Rubino[3], Giuseppina Ruggiero[3], Marco Romano[5], Maria Triassi[2], Vittorio Ricci[1*] and Raffaele Zarrilli[2,6*]

Med Microbiol Immunol
DOI 10.1007/s00430-016-0450-5

CrossMark

ORIGINAL INVESTIGATION

Effective immunosuppression with dexamethasone phosphate in the *Galleria mellonella* larva infection model resulting in enhanced virulence of *Escherichia coli* and *Klebsiella pneumoniae*

Miquel Perez Torres[1,2] · Frances Entwistle[1] · Peter J. Coote[1]

Virulence

Taylor & Francis
Taylor & Francis Group

Virulence

ISSN: 2150-5594 (Print) 2150-5608 (Online) Journal homepage: http://www.tandfonline.com/loi/kvir20

Galleria mellonella infection models for the study of bacterial diseases and for antimicrobial drug testing

Catherine Jia-Yun Tsai, Jacelyn Mei San Loh & Thomas Proft

+ MODEL

Journal of Microbiology, Immunology and Infection (2016) xx, 1–6

Available online at www.sciencedirect.com

ScienceDirect

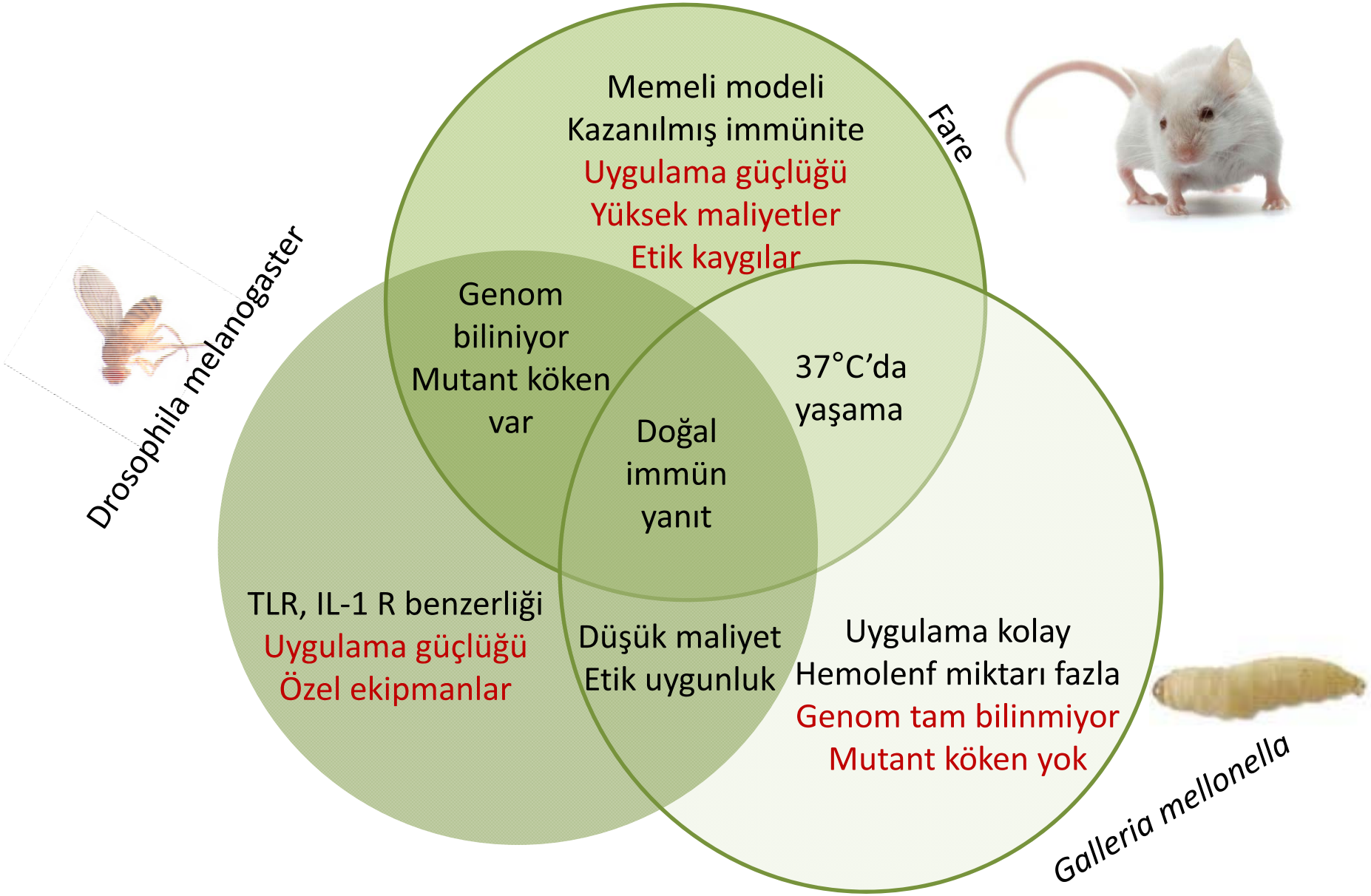
journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Enhanced efficacy of imipenem-colistin combination therapy against multiple-drug-resistant *Enterobacter cloacae*: *in vitro* activity and a *Galleria mellonella* model

Haifei Yang [a,e], Guosheng Chen [a,e], Lifen Hu [a], Yanyan Liu [b,c], Jun Cheng [a], Ying Ye [a,b,c], Jiabin Li [a,b,c,d,*]

Fare, *Drosophila* ve *G. mellonella* modellerinin üstünlük ve kısıtlılıkları



Ann Ist Super Sanità 2013 | Vol. 49, No. 1: 9-17
DOI: 10.4415/ANN_13_01_04

Invertebrate welfare: an overlooked issue

Kelsey Horvath[a], Dario Angeletti[b], Giuseppe Nascetti[b] and Claudio Carere[b]

[a] *Royal (Dick) School of Veterinary Studies, University of Edinburgh, Roslin, Scotland, UK*

[b] *Centro Ittiogenico Sperimentale Marino (CISMAR), Dipartimento di Scienze Ecologiche e Biologiche, Università degli Studi della Tuscia, Tarquinia (VT), Italy*

Abstract

While invertebrates make up the majority of animal species, their welfare is overlooked compared to the concern shown to vertebrates. This fact is highlighted by the near absence of regulations in animal research, with the exception of cephalopods in the European Union. This is often justified by assumptions that invertebrates do not experience pain and stress while lacking the capacity for higher order cognitive functions. Recent research suggests that invertebrates may be just as capable as vertebrates in experiencing pain and stress, and some species display comparable cognitive capacities. Another obstacle is the negative view of invertebrates by the public, which often regards them as pests with no individual personalities, gastronomic entities, or individuals for scientific experimentation without rules. Increasingly, studies have revealed that invertebrates possess individual profiles comparable to the personalities found in vertebrates. Given the large economic impact of invertebrates, developing certain attitude changes in invertebrate welfare may be beneficial for producers while providing higher welfare conditions for the animals. While the immense number and type of species makes it difficult to suggest that all invertebrates will benefit from increased welfare, in this review we provide evidence that the topic of invertebrate welfare should be revisited, more thoroughly investigated, and in cases where appropriate, formally instituted.

Key words
- invertebrates
- animal welfare
- stress
- pain
- behaviour

Galleria mellonella enfeksiyon modelleri;

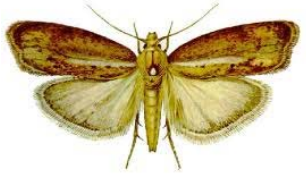
Tüm genom diziliminin bilinmemesi ve mutant türlerinin olmaması kısıtlılıkları olmakla birlikte ;

- Ucuz, kolay, hızlı bir yöntem olması
- Etik kaygıların daha az olması
- Karşılaştırmalı çalışmalardan elde edilen verilerin tutarlı olması nedeniyle

G. mellonella;

- Mikrobiyal virülans faktörlerinin karakterizasyonu ve identifikasyonunda,
- Antimikrobiyallerin etkinliklerinin test edilmesinde
- Toksisite çalışmalarında

Güvenilir ve alternatif model



Sonuç olarak;

- Hiçbir model mükemmel değildir.
- İnsan hastalığını fizyolojik, biyolojik ve immünolojik yönleri açısından birebir yansıtamaz.
- Ancak her bir model spesifik güçlü yönlere sahiptir ve özellikle faz öncesi çalışmalarında son derece değerli veriler sunmaktadır.

İlginiz için teşekkür ederim.