# Biotherapy: Medicinal Maggots and Invertebrate Immunology from the Clinician's Perspective

Ronald A. Sherman and Edwin L. Cooper

Biotherapy is the term used to denote the practice of using live animals to treat or diagnose illness. The term, and the formal discipline, are only about 30 years old, but the practice itself dates back thousands of years. The use of leeches and honey bees, for example, can be traced back to ancient Greek, Egyptian, Persian, and Asian societies (Gileva and Mumcuoglu 2013; Kim 2013). Biotherapy encompasses a variety of living creatures, from microbes to mammals (Fig. 1). Examination of one of these modalities, maggot therapy, offers an opportunity to examine how invertebrate immunology and physiology have been harnessed to benefit human health.

Maggot therapy, also known as maggot debridement therapy (MDT), larval therapy, biodebridement, and biosurgery, is the application of live fly larvae to wounds in order to aid in wound debridement (cleaning), disinfection, or healing. A maggot infestation on a living vertebrate host is called myiasis. When that infestation is limited to a wound, it is called wound myiasis. Maggot therapy is basically a therapeutic wound myiasis, controlled to optimize efficacy and safety (Sherman et al. 2013). We control myiasis by carefully selecting the species and strain of fly (Table 1), disinfecting the larvae, using special dressings to maintain the larvae on the wound, and integrating quality control measures throughout the process.

Maggot therapy treats chronic wounds through three main actions: debridement (removal of dead tissue and debris), disinfection, and stimulation of healthy tissue growth (Sherman 2014). These actions are brought about through the maggots' digestive secretions/excretions and through the physical action of the maggots

R. A. Sherman (✉)
BioTherapeutics, Education & Research (BTER) Foundation, Irvine, CA, USA
e-mail: RSherman@uci.edu

E. L. Cooper
Laboratory of Comparative Immunology, Department of Neurobiology, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA



E. L. Cooper (ed.), *Advances in Comparative Immunology*,
https://doi.org/10.1007/978-3-319-76768-0_30

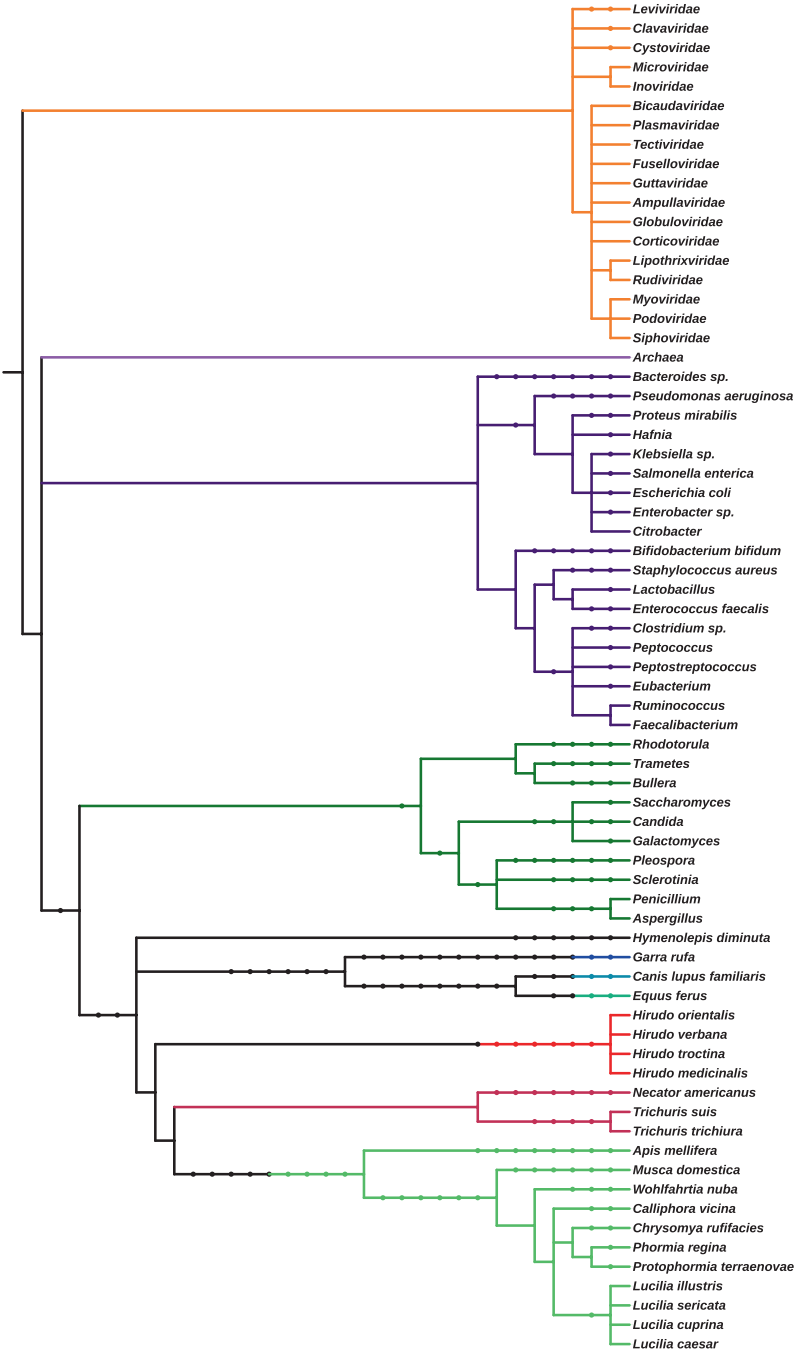


**Fig. 1** Phylogenetic diagram of most commonly used biotherapeutic animals. Major clades include viruses, archaea, bacteria, fungi, platyhelminths, annelids, nematodes, insects, cyprinids (carp), canines, and equines

**Table 1** Fly species (Order: Diptera) that have been used in maggot therapy

| Family | Species |
|---|---|
| Calliphoridae | |
| | *Calliphora vicina* |
| | *Chrysomya rufufacies* |
| | *Lucilia caesar* |
| | *Lucilia cuprina* |
| | *Lucilia illustris* |
| | *Lucilia sericata* |
| | *Phormia regina* |
| | *Protophormia terraenovae* |
| Sarcophagidae | |
| | *Sarcophaga haemorrhoidalis* |
| | *Sarcophaga bullata* |
| | *Wohlfahrtia nuba* |
| Muscidae | |
| | *Musca domestica* |

After Sherman et al. (2013)

crawling about the wound bed. Maggot debridement is thorough and precise. It is accomplished, in part, through the proteolytic action of the maggots' digestive enzymes, liquefying the necrotic wound tissue but not the viable tissue. The maggot's spined body also aids in debridement by dislodging dead cells and debris.

Microbial killing was extensively reviewed by Nigam and associates (Nigam et al. 2006a, b). In the decade since, we have come to learn that *Lucilia sericata* secretions/excretions not only kill bacteria in cultures but also dissolve and inhibit the formation of biofilms (Cazander et al. 2009, 2010; Bohova et al. 2014). It was long assumed that medicinal maggots produced antimicrobial peptides like many other insects, especially given the fact that species members, used medicinally, would need to protect themselves from microbes that abound in their natural environments: corpses, feces, and other decaying organic matter. A variety of antimicrobial peptides have now been identified, and some have been completely characterized, including lucifensin (Cerovsky et al. 2011), lucimycin (Pöppel et al. 2014), alloferons (Chernysh et al. 2002), and others (Ratcliffe et al. 2014).

Medicinal maggots alter the immune system of the host as well. Clinically, maggot therapy has been associated with decreased inflammation, though this may in part be merely a result of the antimicrobial and debriding actions that also reduce inflammatory stimuli. Recently, laboratory studies demonstrated that medicinal maggots might suppress the immune response directly by affecting the complement cascade. By combining secretions/excretions from *L. sericata* larvae with serum from preoperative (healthy) and postoperative (immune-activated) patients, Cazander et al. (2012) demonstrated that the maggot excretions reduced complement activation up to 99.9%, via all pathways, breaking down C3 and C4 proteins in a cation-independent, temperature-tolerant manner. Dauros Singorenko and coworkers (2017) demonstrated that maggot excretions/secretions upregulated gene expression in several human wound cell types in vitro, especially monocytes, and partially reduced the interleukin 8 transcription otherwise seen in response to bacterial lipopolysaccharide exposure.

In 2004, medicinal maggots became the first live animal to be granted marketing clearance by the US Food and Drug Administration (FDA) (Sherman 2014). Leeches (*Hirudo medicinalis*) are the only other live animal cleared by the FDA for marketing in the USA (Mumcuoglu 2014).

The use of these animals as food or nutritional supplements and the use of their tissues and extracts are not considered to be biotherapies (since it is not the living animal that is used). But their medicinal benefits may very well be based, at least in part, on some of the same biochemical and immunological mechanisms of action. For example, leech saliva has been shown to contain antimicrobial, anti-inflammatory, and anticoagulant proteins, useful in treating osteoarthritis (Michalsen et al. 2003, 2008; Andereya et al. 2008; Stange et al. 2012; Cooper and Mologne 2016), and a few hirudin-based drugs have been approved as anticoagulants (Eldor et al. 1996; Fields 1991). With continued research, the list of medicinal animals and animal products making their way into mainstream medical practice should continue to grow.

## References

Andereya S, Stanzel S, Maus U, Mueller-Rath R, Mumme T, Siebert CH, Stock F, Schneider U (2008) Assessment of leech therapy for knee osteoarthritis: a randomized study. Acta Orthop 79:235–243

Bohova J, Majtan J, Majtan V, Takac P (2014) Selective antibiofilm effects of *Lucilia sericata* larvae secretions/excretions against wound pathogens. Evid Based Complement Alternat Med 2014:857360

Cazander G, van Veen KE, Bouwman LH, Bernards AT, Jukema GN (2009) The influence of maggot excretions on PAO1 biofilm formation on different biomaterials. Clin Orthop Relat Res 467:536–545

Cazander G, van de Veerdonk MC, Vandenbroucke-Grauls CM, Schreurs MW, Jukema GN (2010) Maggot excretions inhibit biofilm formation on biomaterials. Clin Orthop Relat Res 468:2789–2796

Cazander G, Schreurs MW, Renwarin L, Dorresteijn C, Hamann D, Jukema GN (2012) Maggot excretions affect the human complement system. Wound Repair Regen 20:879–886

Ceřovský V, Slaninová J, Fučík V, Monincová L, Bednárová L, Maloň P, Stokrová J (2011) Lucifensin, a novel insect defensin of medicinal maggots: synthesis and structural study. Chembiochem 12:1352–1361

Chernysh S, Kim SI, Bekker G, Pleskach VA, Filatova NA, Anikin VB, Platonov VG, Bulet P (2002) Antiviral and antitumor peptides from insects. Proc Natl Acad Sci U S A 99:12628–12632

Cooper EL, Mologne N (2016) Exploiting leech saliva to treat osteoarthritis: a provocative perspective. J Tradit Complement Med 7:367–369

Dauros Singorenko P, Rosario R, Windsor JA, Phillips AR, Blenkiron C (2017) The transcriptional responses of cultured wound cells to the excretions and secretions of medicinal *Lucilia sericata* larvae. Wound Repair Regen 25:51–61

Eldor A, Orevi M, Rigbi M (1996) The role of the leech in medical therapeutics. Blood Rev 10:201–209

Fields WS (1991) The history of leeching and hirudin. Haemostasis 21(Suppl 1):3–10

Gileva OS, Mumcuoglu KM (2013) Hirudotherapy. In: Grassberger M, Sherman RA, Gileva OS, Kim CMH, Mumcuoglu KY (eds) Biotherapy – history, principles and practice: a practical guide to the diagnosis and treatment of disease using living organisms. Springer, Heidelberg, pp 31–76

Kim CMH (2013) Apitherapy – bee venom therapy. In: Grassberger M, Sherman RA, Gileva OS, Kim CMH, Mumcuoglu KY (eds) Biotherapy - history, principles and practice: a practical guide to the diagnosis and treatment of disease using living organisms. Springer, Heidelberg, pp 77–112

Michalsen A, Klotz S, Lüdtke R, Moebus S, Spahn G, Dobos GJ (2003) Effectiveness of leech therapy in osteoarthritis of the knee: a randomized, controlled trial. Ann Intern Med 139:724–730

Michalsen A, Lüdtke R, Cesur O, Afra D, Musial F, Baecker M, Fink M, Dobos GJ (2008) Effectiveness of leech therapy in women with symptomatic arthrosis of the first carpometacarpal joint: a randomized controlled trial. Pain 137:452–459

Mumcuoglu KY (2014) Recommendations for the use of leeches in reconstructive plastic surgery. Evid Based Complement Alternat Med 2014:205929

Nigam Y, Bexfield A, Thomas S, Ratcliffe NA (2006a) Maggot therapy: the science and implication for CAM part I-history and bacterial resistance. Evid Based Complement Alternat Med 3:223–227

Nigam Y, Bexfield A, Thomas S, Ratcliffe NA (2006b) Maggot therapy: the science and implication for CAM part II-maggots combat infection. Evid Based Complement Alternat Med 3:303–308

Pöppel AK, Koch A, Kogel KH, Vogel H, Kollewe C, Wiesner J, Vilcinskas A (2014) Lucimycin, an antifungal peptide from the therapeutic maggot of the common green bottle fly *Lucilia sericata*. Biol Chem 395:649–656

Ratcliffe N, Azambuja P, Mello CB (2014) Recent advances in developing insect natural products as potential modern day medicines. Evid Based Complement Alternat Med 2014:904958

Sherman RA (2014) Mechanisms of maggot-induced wound healing: what do we know, and where do we go from here? Evid Based Complement Alternat Med 2014:592419

Sherman RA, Mumcuoglu KM, Grassberger M, Tantawi TI (2013) Hirudotherapy. In: Grassberger M, Sherman RA, Gileva OS, Kim CMH, Mumcuoglu KY (eds) Biotherapy - history, principles and practice: a practical guide to the diagnosis and treatment of disease using living organisms. Springer, Heidelberg, pp 5–29

Stange R, Moser C, Hopfenmueller W, Mansmann U, Buehring M, Uehleke B (2012) Randomised controlled trial with medical leeches for osteoarthritis of the knee. Complement Ther Med 20:1–7