

Topical Treatments for Drug-resistant Infections

New Mexico Tech Drug Discovery Team

New Mexico Tech is looking to partner with a company to bring our compounds to market. The technology and the associated intellectual property are available for exclusive license, and we are ready to support the partner company in these efforts. The overall goal of this project is to develop IM9, a topically-applied drug, which will effectively kill a broad spectrum of otherwise untreatable drug-resistant bacteria and mitigate sepsis.

1. Multi-drug resistant bacteria are an increasing global threat. In general, bacteria first infect a wound in the skin; the infection becomes life-threatening if drug-resistant bacteria spread into circulation. Pathogens of highest concern include:
 - Methicillin-Resistant *Staphylococcus aureus* MRSA (skin, lung, blood infections)
 - Vancomycin-resistant *Enterococcus* VRE (gut, urinary tract & wound infections)
 - Multi-drug resistant *A. baumannii* (wound infections; of grave concern to the US military)
 - Multi-drug resistant *P. aeruginosa* (burn wounds, cystic fibrosis, UTI)
 - Carbapem-resistant enterococcus (CRE, the latest drug-resistant scourge)
 - *M.abscessus* (post-surgery infections, epidemic among cystic fibrosis patients)
 - *S. pyogenes* (dreaded flesh-eating bacteria)
 - *S. mutans* (dental cavities)

2. Over the past five years, our New Mexico Tech research team designed, synthesized and extensively *in vitro* tested a small synthetic compound (IM9) that:
 - synergizes with seven different classes of clinically-used antibiotics and enables them to again work at low doses against otherwise drug-resistant bacteria, and
 - is activated by plain white light and becomes directly and exceptionally toxic by itself.

For example: co-treatment of MRSA with IM9 and an antibiotic (e.g. Oxacillin, Norfloxacin, Vancomycin, Tetracycline, Doxycycline, Penicillin G, Dicloxacillin or Tobramycin) results in ~ 8 log MRSA kill compared to any antibiotic alone. In the presence of colistin, IM9 kills ~5 logs of the super-bug CRE; a subsequent 2 minute irradiation with light eradicates the remaining bacteria to a final count of zero. Similar data is available for the other pathogens listed above. Classic, widely-accepted *in vitro* wound models have shown great promise (e.g. 100% kill for MRSA and *A. baumannii*) but further work is needed.

3. IM9 belongs to an NMT-developed large class of structurally analogous compounds that display a combinatorial repertoire of favorable properties. Some potent synergizers are not photo-activatable while others are directly active (e.g. to vaginal & thrush-causing *C.albicans* fungus).
4. A small scale preliminary animal study with an IM9 analog showed no toxicity in mice well above the anticipated therapeutically-relevant doses. That same analog showed remarkably favorable metabolic and pharmacokinetic *in vitro* profile. Large-scale production of IM9 is not yet in place but is readily achievable with funding support. Next steps would focus on animal studies, starting with various infected wound models and conducted by an external paid-for expert facility.
5. IM9 appears to possess multiple mechanisms of action: inhibition of bacterial stress response, inhibition of drug efflux pumps, and production of singlet oxygen. Further studies are planned to elucidate these co-existing and potentially overlapping mechanisms, including apparent resistance to resistance.

6. This work is in the pre-clinical phase and filed for patent protection in mid-2016 (Patent: US 20160304453 A1); additional related patents are in the pipeline for this ongoing, multi-year project.



NMT logo on MRSA-inoculated agar plate.
All cells were exposed to non-toxic concentration of IM9 and selective killing accomplished by shining plain white light for 2 minutes only on the chosen areas.