Bugworks is a validation of Cellworks simulation in silico Technology Platform where its Bugworks Microbial Platform (BMP) combines functional proteomics with sophisticated semiconductor design engineering to model and manipulate various bacterial systems. Bugworks is a timely entry to the pharma/biotech universe as it is focused on addressing the WW growing problem of antibiotic Resistance and search for “drugs for bad bugs” for Serious hospital infections. The company has secured around $1.5m of combined funding (personal, grants) within six months of inception. Considering the global importance of developing new drugs for serious infections we expect it to attract strategic investors as its portfolio matures.

**Therapy focus- Serious Hospital Infection**- Misuse/overuse of antibiotics accelerated antimicrobial resistance (AMR) and has resulted in the emergence of “super bugs” which are posing life threatening challenges worldwide. Many of the advances in medical treatment like cancer therapy; organ transplants etc. would go waste if the ability to fight infections during the treatment were not available. If that ability is lost, the gains made in life-improving modern medical advantages will be lost creating a situation of - “one step forward two step back”. Novel approaches are immediately required to combat these “super infections” warranting need for new classes of antibiotics, new approaches to develop antibiotics and other preventive/therapeutic approaches. The GAIN act and QIDP designation for new drugs for serious infections in US have been established to incentivize and accelerate the pace of development of new drugs WW including India. Also the environment is very favourable (regulatory, grants) for developing drugs for these bad bugs.

**Technology Platform**

Bugworks/ Micorbial Platform (BMP) originated at Cellworks where the Cellworks' ProtoBuG platform included all the essential central metabolic and signaling pathways such as Glucose, Glycerol & Acetate transport systems and their metabolism (Glycolysis, TCA, Pentose Phosphate Pathway etc.), Fatty acid metabolism, Protein biosynthesis, Amino acid metabolism pathways, Cell wall synthesis and
nucleotide synthesis pathways. The ProtoBuG technology was comprised of 9 major metabolic networks, more than 500 biochemical & signaling reactions and almost 130 operon-controlled genes that are responsible for the transcription of key metabolic enzymes. This technology supports multi-operating environment conditions like Glucose and Acetate minimal medium as nutrient source and varying Oxygen levels. The system is compatible for both the batch culture as well as the continuous culture experimentation. This thereby enables different types of perturbation analyses to be conducted and thereby benchmarking of a wide set of metrics such as Biomass Index and new markers of death like NAD/NADH Ratio. With bacterial systems, being less complex compared to some of the higher organisms, the Biomass is considered as a direct measure of growth, where the metabolic flux distribution aids the growth of an organism.

The BMP model of \textit{E. coli} is modular and adaptable to tackle a broad spectrum of pathogens that afflict large communities, hospitals and ICUs alike. The platform’s ability to deliver (Figure 1) was validated when the Bugworks team (while a part of Cellworks group) successfully discovered drug combinations for treating MDR and XDR-TB in collaboration with AstraZeneca, funded by Wellcome Trust, and the drug – NC4 is likely to enter clinical trials in 2015.
The company’s approach (Figure 2) to develop new drugs to serious infections is through -

- Resurrection of Antibiotics- Enhance Efficacy & Mitigate resistance
- Discover novel mechanisms -Beat efflux, Disrupt biofilms

**Figure 1**

Bugworks

**DRUG DEVELOPMENT SUCCESS FOR TB**

**NC4**: Discovery of novel combinations from the pool of existing drugs for treating Tuberculosis

- Successful translation from computational model to Animal studies
- Two triplets and five quartets better than the standard TB drug regimen
- Poised for Clinical Trials in TB patients

**WELLCOMETRUST FUNDED (1 MUSD)**

**COLLABORATION: CELLWORKS + ASTRAZENECA**

Source: MP Advisors, Company Reports

The company’s approach (Figure 2) to develop new drugs to serious infections is through -

- Resurrection of Antibiotics- Enhance Efficacy & Mitigate resistance
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**Figure 2**

Bugworks

**GOING WAY FORWARD**

**FOCUS: HEALTHCARE ASSOCIATED INFECTIONS**

**Gram negative bacteria**
- Acinetobacter baumannii
- Burkholderia cepacia
- Carbapenem-resistant Enterobacteriaceae
- Klebsiella pneumoniae
- Pseudomonas aeruginosa

**Gram positive bacteria**
- Methicillin-resistant Staphylococcus aureus (MRSA)
- Vancomycin-resistant Staphylococcus aureus (VRSA)
- Clostridium difficile
- Vancomycin-resistant Enterococci (VRE)

Central line-associated bloodstream infections (CLABSI)
- Catheter-associated infections
- Ventilator-associated pneumonia
- Surgical site infections
- Gastrointestinal infections

Source: MP Advisors, Company Reports
Background:

**Running Out of Drugs to Treat Serious Gram-Negative Infections**

Among all of the bacterial resistance problems, gram-negative pathogens are particularly worrisome, because they are becoming resistant to nearly all available drugs considered for treatment. The most serious gram-negative infections are healthcare-associated, and the most common pathogens are Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter*. The threat is not to the same extent, for some of the gram-positive infections (e.g., *Staphylococcus* and *Enterococcus*).

**Most Negative**

**Carbapenem-resistant Enterobacteriaceae (CREs).** The rapid increase in CREs has been compared to a risk as serious as terrorism!. CREs cause bladder, lung and blood infections that can spiral into life-threatening septic shock. They evade the action of almost all antibiotics — including the carbapenems, In the United States, these bacteria have been found in 4% of all hospitals and 18% of those that offer long-term critical care. An analysis carried out in the United Kingdom predicts that if antibiotics become ineffective, everyday operations such as hip replacements could end in death for as many as one in six !

**Need of the Hour- New Targets= New Antibiotic Class**

In the next decade antibiotics with novel MOA if approved should be able to offer some respite to the emerging threat of resistance. Innovation is needed, not only for the development of new antibiotics, but also for combination therapy. By targeting many mechanisms of resistance simultaneously, combination therapy might help slow the emergence of resistance. Besides antibiotics, new treatment strategies under investigation include methods to stop plasmid replication or resistance mechanisms such as efflux pump inhibitors. bacteriophage treatment—used in the 1920s and later in the Soviet era—is being investigated as another potential strategy, but regulatory requirements for these types of drugs are challenging, and their use might not extend to life-threatening infections. Innovation is coming mostly from small biotech/research labs but now the large pharma are slowly gearing to address the problem through collaborations or outright acquisitions of the innovators.

The GAIN act has been specially laid out to encourage innovation in this sector and save lives as well as cut down costs incurred for hospitalization and critical care.
The GAIN Act

- On June 26, 2012, the US Senate overwhelmingly (92-4) passed the FDA Safety and Innovation Act (FDASIA), which reauthorizes the Prescription Drug User Fee Act (PDUFA) for the fifth time. Within PDUFA-V (Title VIII / Sections 801 through 806) is a section entitled "Generating Antibiotic Incentives Now (GAIN)". The GAIN Act is designed to provide pharma and biotech companies with incentives to develop new innovative antibiotics for the treatment of life-threatening infectious diseases caused by drug resistant pathogens. These pathogens are defined in the act, but primary consists of resistant gram positive pathogens, including MRSA, vancomycin-resistant Staphylococcus and enterococcus, multi-drug resistant gram negative bacteria, including *Acinetobacter*, *Klebsiella*, *Pseudomonas*, and *E. coli* species, multi-drug resistant tuberculosis, and *Clostridium difficile*.

- Among the provisions listed in the GAIN Act, sponsors developing Qualified Infectious Disease Products (QIDPs) may benefit from the following incentives:
  - **Exclusivity**: Sponsors filing a NDA that qualifies as QIDPs would be issued 5 years of market exclusivity in addition to the standard 5 years of exclusivity for a new chemical entity under Hatch Waxman. Therefore, QIDPs would qualify for 10 years of market exclusivity concurrent with or without patent protection.
  - **Priority Review**: NDAs for QIDPs would qualify for Priority Review by the FDA, reducing the standard 12 month review period to 8 months.
  - **Fast Track Status**: Sponsors of QIDPs would be provided with early and frequent communications with the FDA, in addition to the typical review and communication opportunities, potentially speeding the path from PhI to NDA filing.