Format for CSR Proposals of Social Relevance

1. Title of Project: Bone graft substitutes for segmental defects in long bones

2. Background/Motivation: The most common lower extremity long bone fractures are tibia shaft fractures. They make up about 17% of all lower extremity fractures with an annual incidence of 3.4 per 100 000. Most of the fractures are due to road traffic accidents. There are mainly two types of injuries, i.e., open (compound) and closed injury. Open injuries are more grievous due to a lot of blood loss and a high infection rate. There is bone loss in open injuries.

The available management options for open tibia fractures with bone loss are as follows.

1. 2 staged surgery – debridement + external fixation for tibia fracture, and then in second stage, an autograft is placed for accommodating the bone loss and fix with an orthopedic implant
2. 2 staged surgery – debridement + placing antibiotic-impregnated cement at the bone loss region (which acts as a spacer). In the second stage, by three months, a periosteum-like layer forms around the spacer. So, this layer needs to be sliced open, and an autograft is placed by the Masquelet technique, and the periosteum is closed.
3. Commonly in the second stage surgery, other than autograft, commonly taken from the anterior iliac crest, allografts from bone banks and bone graft substitutes are also used.

PROBLEMS

1. Autograft site – Autograft is available but can be harvested only in very small pieces. Many complications are seen at the anterior iliac crest site, i.e., infections, superficial seromas, hematomas, hernias, vascular injuries, nerve injuries, iliac wing fractures
2. Allograft from the bone bank – these cadaver bone grafts take almost 18 months to heal, i.e., to incorporate and remodel. So, the duration is very long, which is a significant disadvantage. Also, it has a high rejection rate, high infection rate, and it's not cost-effective
3. Bone graft substitutes (artificial bone graft) – only small cubes (2 cm*1 cm) are available in the market, but they are brittle and have insufficient strength.

3. Objectives of the project:

The autograft needs to be replaced with a synthetic bone graft that may contain BMPs (bone morphogenic proteins), stem cells, and antibiotics to treat the large bone defect and prevent infection. Furthermore, the chemical properties should be like the native bone, and the graft needs to stable there at the implanted site for one year at least, besides being non-toxic, having good strength, and porous supporting bone tissue ingrowth.

To fulfill the above requirements, the following objectives are set.

1. Development of a novel biomimicking composite formulation for 3D printing of bone graft substitute
2. Devising a strategy to encapsulate the gentamycin antibiotic and evaluation its release profile
3. Collection of patient CT data and generation of CAD model of the defect site and 3D printing of bone graft with antibiotic-loaded composite
4. In vitro and in vivo evaluation of the generated bone graft substitute to evaluate the regeneration potential of the bone graft

4. Brief Methodology:

A novel biomimicking composite formulation consisting of PCL, silk, and hydroxyapatite will be made for 3D printing of bone graft substitute. We have already developed a composite of PCL and silk and checked its bone regeneration ability. We would like to include hydroxyapatite as it would make the composite bone indictive.

A strategy to encapsulate the gentamycin antibiotic within the composite will be devised, and its release profile will be evaluated to assess the release kinetics. It is known that the antibiotic release is required to be present for 8-12 weeks.

To print a defect-specific bone graft, patient CT data will be collected from our collaborators, and a CAD model will be generated using modeling software. The CAD model will be used for 3D printing of bone graft substitute with the antibiotic-loaded composite formulation.

In vitro evaluation of the generated bone graft substitute will be done to assess its cellular response and osteoconductive and osteoinductive properties. To evaluate the regeneration potential of the bone graft, a long-bone defect model in a rabbit will be selected, where a 1 cm defect in a long bone will be created, and a 1 cm bone graft substitute of a similar exact shape will be implanted. Different multimodal characterization will be done to assess the bone tissue regeneration by histopathology at 3, 6, 9, 12 months, observation under micro-CT to assess bone mineralization at different time points. If it remodels and maintains for one year without absorbing completely, it gives structural support as an autograft.

5. Target population/Beneficiaries: Many people undergoing accidents and trauma and having long bone fractures will be benefitted from this study. The bone graft substitute would decrease the duration of the surgery, reduce infection rate, and help patients recover faster.

6. Expected Outcome/Deliverables:

7. Timeline and Budget:

	Year 1	Year 2	Year3
Budget (in Rs lakhs)	10	10	10
Milestones	Development of a novel biomimicking composite formulation for 3D printing of bone graft substitute Devising a strategy to encapsulate the gentamycin antibiotic and evaluation its release profile	Collection of patient CT data and generation of CAD model of the defect site and 3D printing of bone graft with antibiotic-loaded composite	In vitro and in vivo evaluation of the generated bone graft substitute to evaluate the regeneration potential of the bone graft

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