# Dinosaurs in space

RELICS FROM THE PAST ——————ULTIMATE SURVIVORS——————230 MILLION YEARS ADAPTION ——————ADD SPACE CONDITIONS


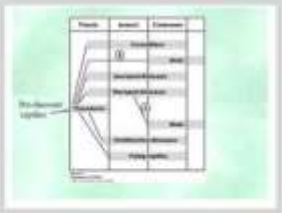

Image sources: freeimages.co.uk, Ornithology 2007, Freeman and Company, NASA.

Adapted from an ESA BIC Noordwijk Open Call **2012**

# space4

**Company ethos: The promotion of animal welfare [and biodiversity] by space science = P.A.W.S.S**

## Division: space4medicine

## Launch project: *dinosaurs-in-space* ©

Pages



~~Contact information~~ of the person(s) who will be in charge of the **direction and strategy:**
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# 1. Executive Summary

Describe your business idea in brief, including the relationship to a space technology and/or space system.

 Drugs fail in the clinic for two basic reasons: they either don't work or they prove to be unsafe. Thus 1 in 10,000 get to market. Result there is a huge push for novel compounds. For example, this year 2012, there has been established the Innovative Medicine Initiative and from that by example the ''*newdrugs4badbugs''*whereby IMI co-funded 111Million Astra and GSK to JOINTLY identify new antibiotics.

 Yet we believe the bottleneck is not the lack of ''novel'' compounds it's a human problem of behaviour and culture. In other words, big pharma often stay in safe fields, for example improving already approved drugs. The second problem is the culture among scientists/clinicians of a need to know more and more about less and less in order to reach a senior status BEFORE they can direct research. This hinders risk taking/cross-disciplinary research by such group leaders in other areas.

 Entrepreneurs do not have this problem. In this project, we simply ask can we decrease these odds against us for drug discovery? Perhaps, by learning from biological systems and **compounds within that have stood the test of time** i.e. compounds from long evolved creatures? We believe yes for the simple reason shown in **Supporting Information 1, figure 1**. In other words creatures have had 200 – 200, 000 times longer to adapt to diseases/environments that also affect humans. These are odds moving in our favour and this project uses these odds and focuses on bone disorder. Encouragingly, dinosaurs have been recently found to exhibit symptoms of human like bone deformation **[Sassoon *et al* , 2012].** Crocodiliae and birds represents our biological link to these creatures. If compound[s] were identified from these highly adapted systems that enhance re-absorption or show inhibitory actions [i.e. antagonistic] to decreased bone formation.

 Such compounds may have medicinal value = potential for patent. For example, osteoporosis treatments, but more over [for IP strategies] the bone loss that occurs in osteogenesis imperfecta [brittle bone disease]. OI is due to a defective collagen gene and encouragingly a recent reference **Pardo *et al,* 2005** indicates that some collagen genes are gravisensitive.

 In space talk, we believe this launch project would be a **translational science : *countermeasure feasibility study*** and in this case it will be done using avian and if obtainable crocodilian osteocellular material. A quick review of current literature and Erasmus Experiment Archive and ESA Feasibility database indicates the way is clear for this or not much competition exists. Moreover, though the knowledge, material and methods are readily available.

 The business part: there is an existing market need but focussing on one compound/product is a bad business strategy. The business idea is building a space agency based drug discovery process with PAWSS values as shown by the other projects. Drives imagination , yet gives the end-user some confidence in the ethics behind it, i.e. enhances consumer confidence **[Supporting information 2a and 2b]** In other words a *collaborative, highly innovative biotech* business model as currently pushed by the big 4 auditing firms.

 Relationship to space tech is the well-documented effect of space habitation on bone mass and demineralization and the use of microgravity simulations and novel developments in micro-g simulations **[Pardo *et al,* 2005; Hill *et al* 2012].** It may also stimulate novel cash flow toward micro-g. For example, some of the most recent cutting edge work on Drosophilla
**gravireceptor** isoforms via magnetic levitation at ESOC has been put on hold due to funding cuts [personal comm.]

# 2. Implementation

 This can be done round the same core milestone planning as the other two projects. Review of prior art → identify supporting/partnering organisation e.g. Naturalis. /DESC etc/ [*also input from some medical research organisation on board would be valuable for later stage clinical trials*] → feasibility study – select animals biological/skeletal material to countermeasure microgravity effect → select microgravity replication method[s] → [e.g. RPM or magnetic levitation set up that was used for Drosophila] → extract target material [RNA/proteins] many very cheap off the shelf kits exist from companies like Invitrogen/Promega to ease procedure → **countermeasure compound identification** use standard apps such as western blot/bandshifting [assuming there are protein-protein interactions] or many upcoming technologies [re biomarkers Bachas *et al*, 2012 or the chips by **Oxford Nanopore**]→ marketing to drug validation companies → re-evaluate business plan/ plus a complete clinical development plan[mock] and prior-art----→ REPEAT CYCLE **[Supporting Information 3].**

 The long-term nature of the work/ ROI means one could get ''scooped'' at any time. Or of course it might not work. So it would be prudent to put the ''DIS process'' to use in other ways. **To plant a flag in this area.** In this case I suggest a competition - as a method to generate awareness of the disease [OI]- excitement and hope. Generating awareness of such Orphan Diseases is a NEED in itself. **This in itself is a noble objective for ESA**. Consider, for example: *The space agency are looking for bones that last longer in space –they think animals like dinosaurs could help- can you help tell them good dinosaurs to use? Draw a picture send in your story of the best DIS……e.g.* X Euros per entry via school…thus cash to charity. Seek advice/assistance and kick-off kids competition for DIS publicity and cash flow. Timing dependent on disclosure issues. For simplicity suggest using *Virgin Money Giving*. Rewards for competition to be space agency based rewards .e.g. expenses paid visit to ESA etc. Putting money to **OI charity /paediatric research** means they must decide how money will be allocated so might get nothing but the whole process may assist in securing future funding on other diseases and recruitment of other workers.

# 3. Space Agency/Company investment opportunity

**1. Primary.** We believe pinning hopes on licensing potential compound and focussing on investing on one potential ''wonder' compound or drug discovery tool/platform [e.g. the yeast two hybrid system] is/was a common biotech mistake [see timeline below]. Thus making the **SPACE4** an investable trademark/brand, a recognisable ethical drug discovery process by following strict criteria [the PAWSS ethos], may be the more logical investment opportunity.

**2. Secondary.** Stages identified for potential investment and very long term ROI for this specific S4M project, i.e. DIS are shown below. The assumptions made are 1] if and only if a HIT can be identified and 2] pharma don't loose interest in it over that timeframe and 3] market still exists in that timeframe [for example due to improvements in bisphosphonates]

 2-3 years – Hits/proof-of-principle obtained which may allow a patent development based on Composition-of-Matter as opposed to Method-of-Use.

 7 years Lead Optimisation e.g. via Argenta Disocvery [Harlow/UK] or Drug Discovery Factory [Netherlands]or KWS Biotest etc or other preferred/recommended drug validation company This may lead to classification as an orphan drug, of course being classified as an orphan drug with marketing authorisation will take longer.

• 12 years Dependent on control of compound at that point, one could team with *Orphan Europe* as a foundation for specialised regulation and aim for market exclusivity for OI but of course not for osteoporosis . Do all this on a risk return basis. As noted the chances are stacked against us thus all investments must bear this in mind. The investment would have to be done on a risk sharing model due to the various entities that need to come on board.

**3. Tertiary Potential ROI opportunity** Extraordinary funding from competition. For example, from toys and apps [e.g. plant V zombies]. This may be good business for a parallel see the toys in space expo. Due to the target partners aim for 95/5 cut on return between charity and S4W. Such examples may seem trivial but can be highly lucrative given they offer large margins. Thus allowing the business to operate whilst waiting on a breakthrough product which of course may never occur.

**4. Quaternary Investment**. As shown above there is also a large grant fund if one can get through the very strict requirements?

5 **Goals** Financially viable, ethical, highly imaginative drug discovery process with PAWSS values at its heart. The implantation of the process could be done with these goals in mind 1) orphan product 2) platform 3) personalized platform 4) personalized product , licence access to technology for additional ROI [repeat cycle] . Or it may just remain focussing on Orphan Diseases products.

## 4. Presentation of the applicant, background and history of the company

Introduction of the entrepreneur Biologist and previously part of a small archaeological start-up company . As a biologist worked in a cystic fibrosis CF centre twenty years ago and it is still with us. Its caused by a mutation called deltaf508 causes a faulty protein. This is inheritable and yields different severities, the cause of CF is similar to a bone disease – *osteogenesis imperfecta* - like CF, OI also still with us. Aware of this it is frustrating that one still sees no bold thinking as we may have seen with Darwin and Flemings predictions [not afraid to be wrong]. So we think '' is it time biotech asked someone else''. Along comes ESA. The long study of all matters bone in space, the availability of space technology and engineers not necessarily associated with drug discovery we believe will bring fresh perspective and approaches to the process, perhaps such as rapid prototyping of a desired method
C) Introduction of the management team Currently focussing on feasibility
D) Support entities ESA, ESA-BIC, DESC? Naturalis[Leiden] ? DDF? Paediatric Research Hospital [flagged up]
E) Vision: The PAWSS values becomes a core part of space technology based drug discovery

# 5 Description of the business idea

A) Business idea: natural product, pre-clinical drug discovery, orphan market. Starting from a small-scale project targeted at a very niche orphan market, with a definite demand, leading up to a streamlined process/platform. The presence of core funding and in-place infrastructure at ESA [such as chemicals, radiation , cell culture , waste processes] and legal know how on their authorized use takes away a great burden to the project allowing focus on the core idea and subsequent business development. There will be an initial orphan disease/drug focus then tool commercialization focus, the tool based on space tech initially - **microgravity.**

B) Core related customer needs: pharmaceutical companies need more lead compounds that have indications that down the pipeline they will be safe, efficient compounds for the clinic.
C) Identified market For this project: Market 1 – drug development companies where possible with a connection to orphan diseases. Market 2 – drug development for more general bone metabolic disorders , required for the worlds growing and an ageing population **[Supporting Information 4].**
D) Unique selling proposition. **USP 1 – PAWSS:** A drug discovery process that proactively promotes animal welfare and promotes the value of biodiversity. **USP 2-** The use of space tech makes discovery process hard to replicate i.e. generics will of course eventually be made but identifying lead compounds with technologies such as micro-g may be much harder to copy cheaply and moreover requires specific know-how

# 5. Description of the product and/or service

A) Description of the product/service and the use For this S4M project [DIS], Product identification: compounds to decrease mineral loss , enhance stability , ease reabsorption

**B) The Space relationship** ESA has gave us ''*crickets in space*'' and ''*fly your thesis*'' Thus *Dinosaurs in Space* business project has strong ESA synergy and sounds a lot more fun. + it just sounds better + Specifically, it gels with many of ESA 's Educational Outreach /Tech Transfer/ Human Space Flight needs. Technically it is a hybrid between HSF : exobiology /biology / human adaption questions as stated in the HSF '' ELIPS'' . In other words it uses the **evolutionary adaption logic** of the exobiology research and marries it with the countermeasure work of biology and human adaption. In the wider context, it immediately addresses the fundamental problem for the EEC [i.e. economic stimulus] and fits in with the EEC Europe 2020 programme and the Innovation Union. Provides a highly tangible benefit to space life sciences research which many see as a little indulgent in the current economic crisis and resulting in the recent cuts to NASA. Or more tellingly even the most recent ESA work on identifying isoforms of gravitational receptors in Drosophila ,using cutting edge micro-g technology, has been put on hold

**C) Non-space benefit** 1) Captures the imagination 2) Inspiration to young and old 3) potential identification of more effective medication for bone wasting diseases in particular under-researched ''orphan diseases'' For example, there are no hits on the EEA database for OI. 4) incorporates space research into drug discovery i.e. . development of streamlined process to do so.

**D) In-depth description of the technology** Simple hybrid of currently available biotech technologies and space technology , cleverly deployed and targeted at an under-researched disease.

E) Stage of development of the product/service The service will be animal welfare / space based drug discovery. The domain *space4medicine* has been purchased , outline plan written out. At the same time we need get going feasibility work. For this many of shelf osteogenesis kits exist. We have unused/underused micro-g platforms. Bring them together with many existing published protocols. Now a question of getting partners on board for example establishing a mini-SAB plus business advice.

F) Research and development . Reviewing prior art. Current indication of prior art microgravity /countermeasures etc can be obtained from Erasmus Experiment Archive. R and D in terms of OI is shown on *Orphanet* . Ongoing always review in light of current developments.

**G) Intellectual property**, *space4wildife* is a registered domain, *space4medicine* is a registered domain . This business process ''*dinosaurs in space*' © belongs to *space4wildif*e and the working project title [as used for a competition title] being *creative, original and , now, fixed* maybe protectable under copyright, but trademark applications will follow **[achieved]** . Due the nature of product sought after patent drafting could begin immediately from kick-off as the claims will be known beforehand. Need licensing agreement of patent holders of pharmaceutical development and delivery systems as any hit would have to be made into medicinei.e. go through various trials. However as stated above, making the ~~S4M~~ [**space4]** an investable trademark/brand , a recognisable ethical drug discovery firm by following strict criteria , may be the more logical investment opportunity.

# 6 Market Analysis

A) The market Service – generating insights into potential areas for novel drugs [the other projects] , detecting novel compounds and delivering pre-clinical data that shows the product may be viable.
B) The market sectors - Based on Standard and Poor's/GICS sector definitions, initially this solution would be located in Health Care 3520 Pharmaceuticals, Biotechnology & Life Sciences.
C) The customer – pharmaceutical ''middle men'' i.e. firms who mediate between university departments and can develop the and validate the compound [proof-of-principle] prior to passing over to FIPCO firms for trials.
D) The geographical coverage – restrict B2B licensing deals to Netherlands or UK drug development companies?

# 7. Business model

A) Supply chain business to business , 1) for low costs discovery , s4m would be operating as a virtual company, then 2) onto firms like Drug Discovery Factory/Argenta Discovery etc for proof of principle , from there 3) to FIPCOs
B) Suppliers S4W, ESA, ESA-BVIT and partners indicated above then to drug development
C) Production 1) Hit detection 2) hit development, using alliance model for access to equipment for proof of principle product
D) Distribution business to business
5.6 Strategy
A) The market approach .....pre-pharma ''partnering market '' preclinical products promoted on basis of a] orphan drug market b] their continued identification/development with respect to PAWSSS - animal welfare/biodiversity. The latter part is thinking of how big pharma may, if it reaches that stage, market the drug.
B) Marketing strategy as part A
C) Sales strategy Risk sharing, percentage of *future sales* if applicable , would depend on downstream market penetration , bottom-line assumption: 1% penetration and product switching occurs.

D) Pricing strategy .

RISK ANALYSIS - SWOT

5.7 Risk analysis

| | Positive | Negative |
|---|---|---|
| INTERNAL | **Strengths**<br>Builds on in-house IP technical expertise<br>Builds on Netherlands biotech start-up strength<br>Large, growing untapped market even a fraction of market should be lucrative,<br><br>The ability to licence out ,development of any potential compound before getting embroiled in regulatory issues more suited to big pharma<br><br>Space knowhow and facilities hard to replicate put hurdle in way of generic copies | **Weaknesses**<br>No SAB established. No dedicated business advisor [ESA-BViT aside] improving management skills<br><br>Starting from scratch, need for raw biological material . Suggested solution local assistance from Naturalis [Leiden] experts .<br><br>Prior art, i.e. a patent may appear blocking path, but one could invent around that .<br>Big pharma saturated by early stage product<br>Downstream may be freedom-to-operate issues. |
| EXTERNAL | **Opportunities**<br>…king to get increase management …human problem unlike cancer , AIDS etc thus addresses a research deficit. Opportunities are global and the "market" will become more frequent as the population grows and ages Thus a continual demand for novel and or refined medications and **novel processes** for their discovery. E,g if an active medicine [lead compound] is not discovered a streamlined service – core competency- could be e.g. *space4medicine* . May attract interest from a FIPCO. | **Threats**<br>Blocked by IP. Scooped by the unknown backroom research laboratory such as the South Korean Biotech Initiative.<br>Pharmaceutical companies are ruthless and will immediately copy and have a bigger war-chest – Solution –NDAs discretion and collaboration<br><br>If an novel compound is discovered the usual threat applies i.e. generic formulas.<br><br>ESA funding gets halted . |

**MILESTONE PLANNING**



5.9 Activity proposal

A) Milestone planning

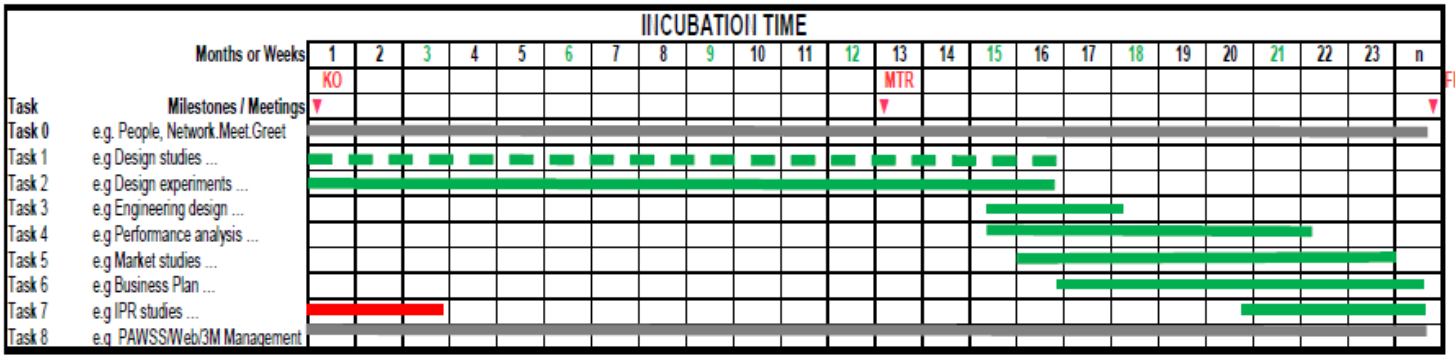



Fig 2: Milestone Planning

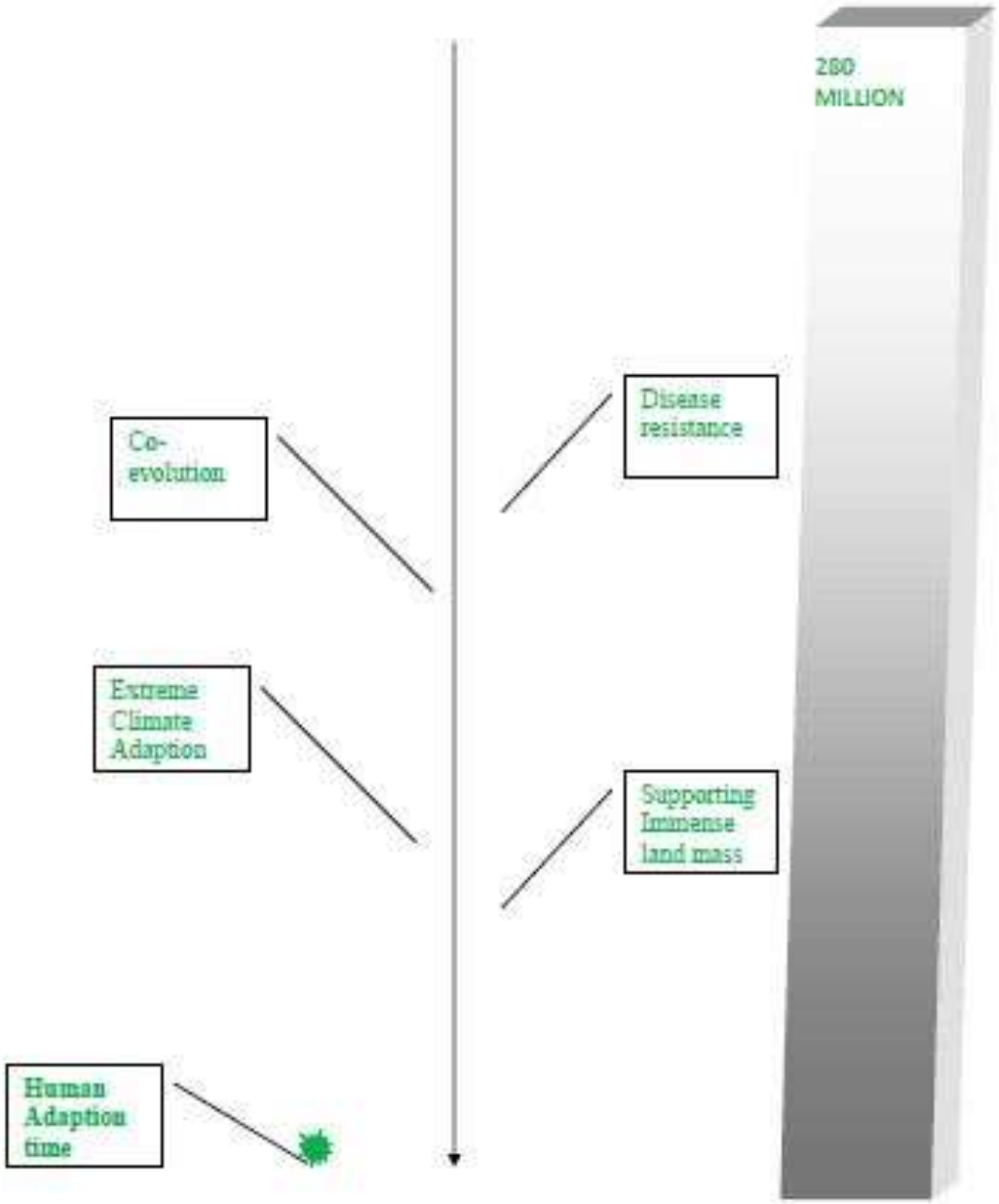
# 8 Supporting Information
## background to implementation

We all know that the effects of micro-g could be a parallel for bone disorders on Earth. For detail [a lot of detail] see the review : A Strategy for Research in Space Biology and Medicine into the Next Century (1998) Space Studies Board (SSB) .
**Problem 1):** Lacking imagination ,may kill off public interest. Yet sustaining this public behaviour and perception is very important in these economic times and is perhaps a failing of scientists failing to see their work in the bigger picture .
**Problem: 2)** strategies therein rely on a heavy use of animals rats, dogs in experiments such as suspension tests, is this the best we can do for animal welfare in so-called ''space-age'' research?
**Problem 3**] Not ''listening'' to biology. i.e. does biology already hold an answer?
There are clues that the logic in this project launch will work. For example a core reference was that of Pardo *et al*, 2005, studying micro-g on preosteoblasts seems to reveal a network of probable protein-protein interactions such as signal transduction proteins. Also see ref therein of Yang *et al,* 2000.
Direct parallels to this work include the EDOS, STROMA 1 and 2 experiments and that of BOP and that of RISTA/ OSTEO or that of the ACTIN projects [all on the EEA ]. Furthermore, on the EEA there are experiments that counter bone-loss with vitamin D and ATP [I assume adenosine triphopshate]. There is also *''topical team''* work looking at evolution in terms of exobiology [radiation resistant micro-organisms, extremophiles such as the EXPOSE-E and TARDIS projects described on the EEA ].This is simply the extension of that *''evolutionary adaption''* logic to this system. I believe this is the first project to bring them together towards translational medicine with a focus on a orphan disease. **Unlike all those projects,** DIS requires no highly expensive flight or pre-flight campaigns.
In terms of developing a drug, the recent patent application [assuming not granted] in 2006 by Pfizer of the use of a vitamin D derivative to treat OI shows both the IP problems and opportunities that may arise.

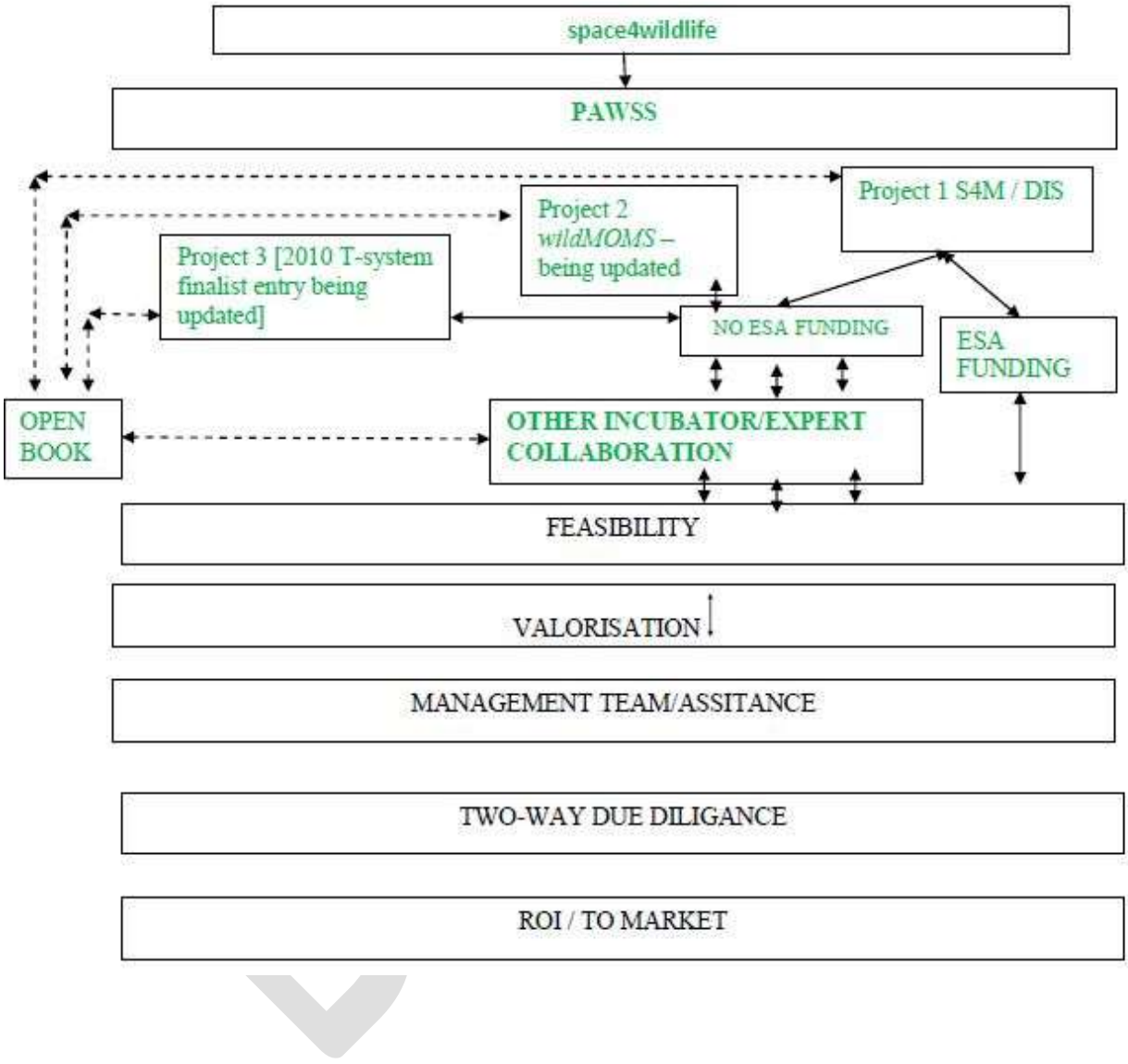
**The prior art?**
Getting back to space, in this next century we have the more recent comparable work [or possible competition dependent on their focus] of the NASA: Avian Development Facility. In particular the investigation of Skeletal Development in Embryonic Quail (ADF-Skeletal] developed from the 2012 NASA Experimental Program to Stimulate Competitive Research (EPSCoR). The Avian Development Facility (ADF) is an incubator designed to house 36 Japanese quail eggs and to fit in a space shuttle middeck locker. Encouragingly, their recent findings might also indicate that the premise in this business launch project is a good one.
Similarly , Brachas *et al* 2011 at NASA are already developing a : *Integrated biomarker diagnostic systems are being developed for monitoring indicators of stress, bone metabolism, and muscle function.* Much of this approach is based on conformational changes of molecules however the group seem unaware that Oxford Nanopore already have a very cheap laptop version of such conformational detection techniques.
**Product Comparable:** Infliximlab i.e. an antibody, or more generally an interacting protein, although this is a natural product it wouldn't fall under patent restrictions as such a purified product doesn't exist freely within the body.
**Company comparable.** The fact that ethos of **Warp Drive** [i.e. chemomeme based discovery] emphasises nature but is regarded as ''new'' emphasises the need to be active [or at least seen to be active] in other areas than drugs. Also it is interesting to note that **Warp Drive** appears to be repeating a previous mistake of relying on prediction / modelling/best guess that led to previous biotech bubble.

## 6. Additional Information

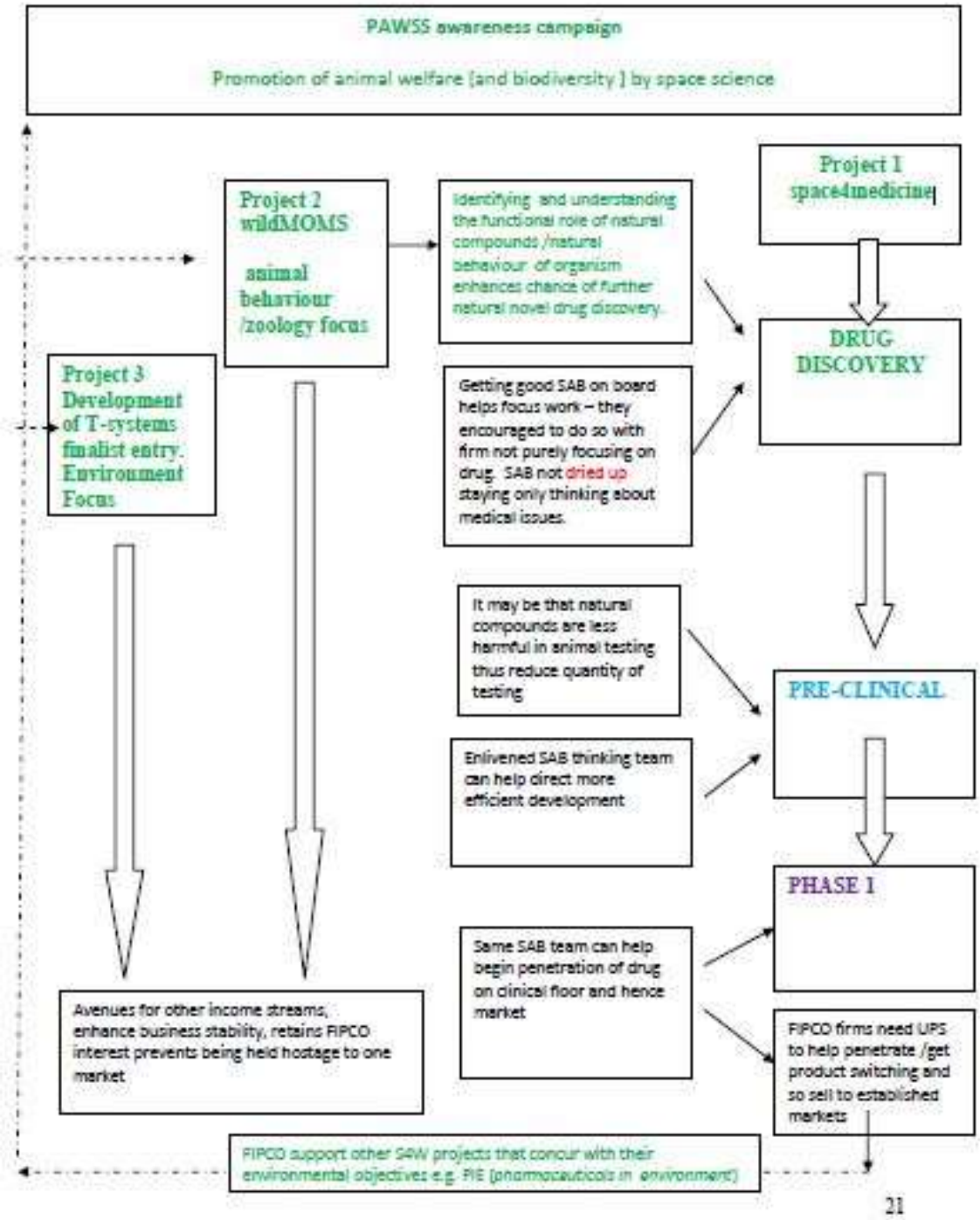
Supporting Information 1: Figure 1. The time humans have had improving resistance to /adaption [nee. *countermeasures*] to evolutionary challenges [not in chronological order] is but a spot compared to dinosaurs and their descendants birds and crocodiles.



Supporting Information 2a: The S4W overall business strategy concurs with future biotech survival needs as analysed by companies such as PriceWaterHouseCoopers :
*S4M being part of a wider "wildlife-utility" based operation gives stability from the outset.*



Supporting Information 2b. How PAWSS values could contribute to the kick off project and core S4M business model, *a new biotech model.*



# 9 Supporting Information
## Methodology details

Impractical to culture primary cells from OI patients , thus need good model, micro-g effect may provide this and thus provide a platform to reveal compounds that alleviate/lesson the detoriation. Currently medication for OI and osteoporosis relies on replace missing compounds – bisphosphonates **[Roldan *et al* 2008].** These have multiple problems detailed elsewhere. Gene therapy is difficult because of gene delivery hurdles. Thus one would aim for **drug differentiation such as** by 1) how it is identified [PAWSS] and 2] hopefully more effective less toxic compounds.

So the choice of approach here is to formally based on acknowledging natures supremacy and may address the problems of novelty and safety for drug discovery. In other words, perhaps we may expect a compound[s] discovered from long evolved creatures, who have been long adapting to stress/diseases/challenges, to be far less toxic when used in pre-clinical animal testing Phase 1 trials before being tested as a drug in humans, see previous graph. Suggested local potential partner for obtaining or identifying sources of such compounds, Naturalis . For drug discovery IP is critical, so this project also builds on inherent technical expertise of available IP consultant. Understand there is two gravimetric devices which are located in laboratory facilities at ESA-ESTEC. One of these devices, the RPM (Random Positioning Machine), is able to create simulated microgravity. The other, the LDC (Large Diameter Centrifuge), generates a 2g effective force. Other options are available at DESC.

Therefore we have **knowledge, materials and methods.** If need be, there exists of the shelf osteoblast cell lines and multiple methods for reproducing micro-g, current work seems lacking direction –simply [complicated] observational studies development, hence giving opportunity for drug discovery-targetted/*translational* focussed approach.

**Briefly Kick-off Methodology** .

Overall note where possible try to **avoid cell lines** as many of these lines have lost their original properties , envisaged first obstacle one may be culturing primary cells without infection. However, isolated mouse bones have been sustained previously therefore there is a protocol to follow.

[Veldhuijzen et al , 1992]

Part 1: Comparison of degradation rates between different cell lines , cultured in six well opti disk as detailed in Pardo *et al,* 2005.

Part 1b. Cell line ‘’Resistance ‘’ to Calcium Ionophores – is that sensible?

Part 2: Countermeasures via crocodilian /avian tissue a] ground up bone tissue 2] co-cultures [a twist on Flemings work/accident].

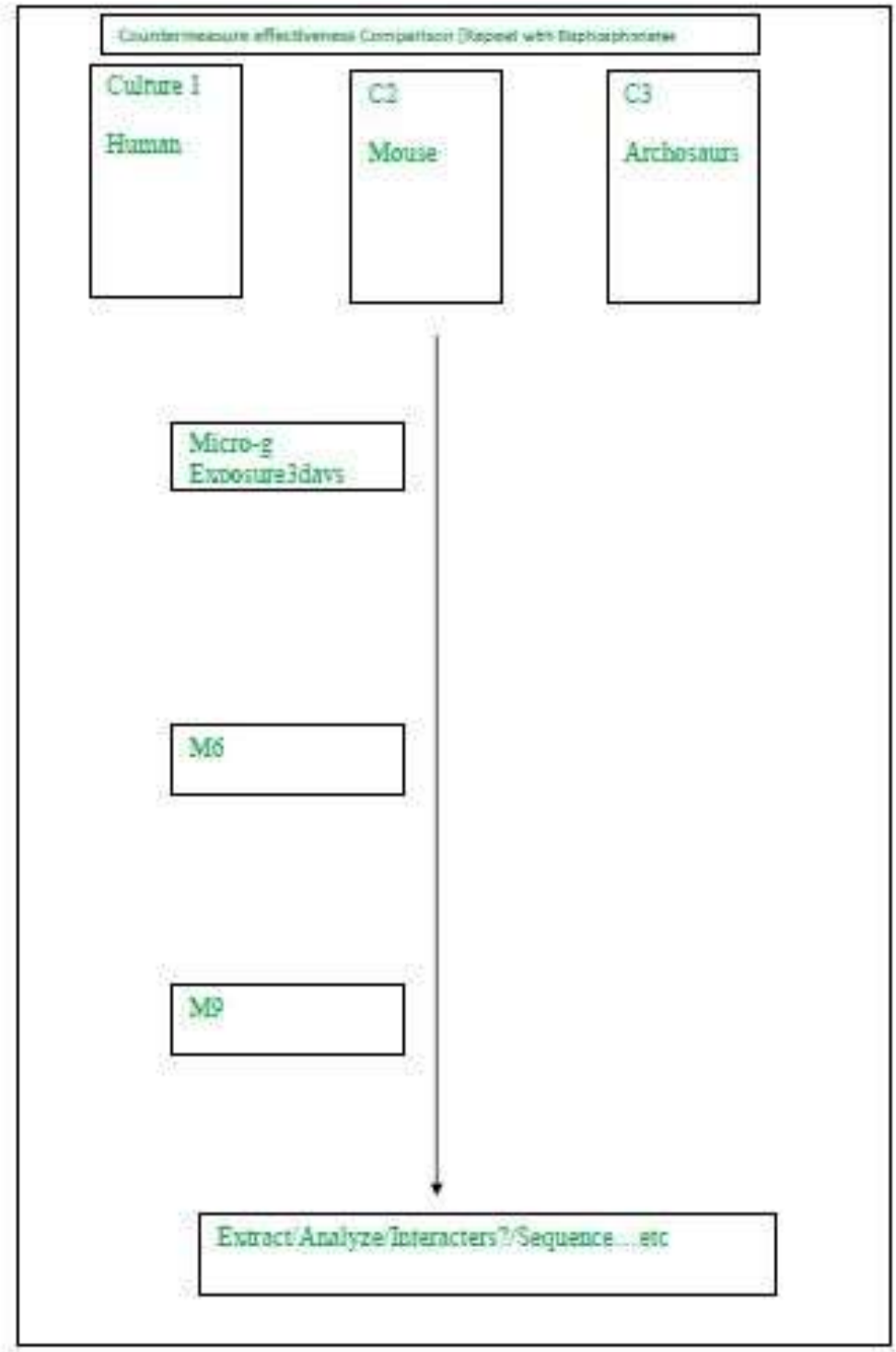
Part 3. If countermeasures effective , then begin **Countermeasure Compound Identification** i.e. collect material, i.e. trypsinise, then RNA/protein kits, identifying [cause[s]s using western blots [bandshift]/ interaction traps and perhaps we could look to nanopore proteomic sequencing, although untested, for low cost/high speed and perhaps they ON may volunteer expertise. This may allow one to cheaply quickly identify novel compounds.

For co-culture if that is successful i.e do the other cells try to rescue the weaker cells then perhaps look to global expression analysis [such as that for levitation of Drosophilla].

**Parallel experiment** : actual bones in magnetic levitation setup, size is a limiting factor in that method

**See Figures 2 and 3 and 4 below.**

Part 1: Comparison of degradation rates between different cell lines , cultured in six well opti disk as detailed in Pardo *et al,* 2005.



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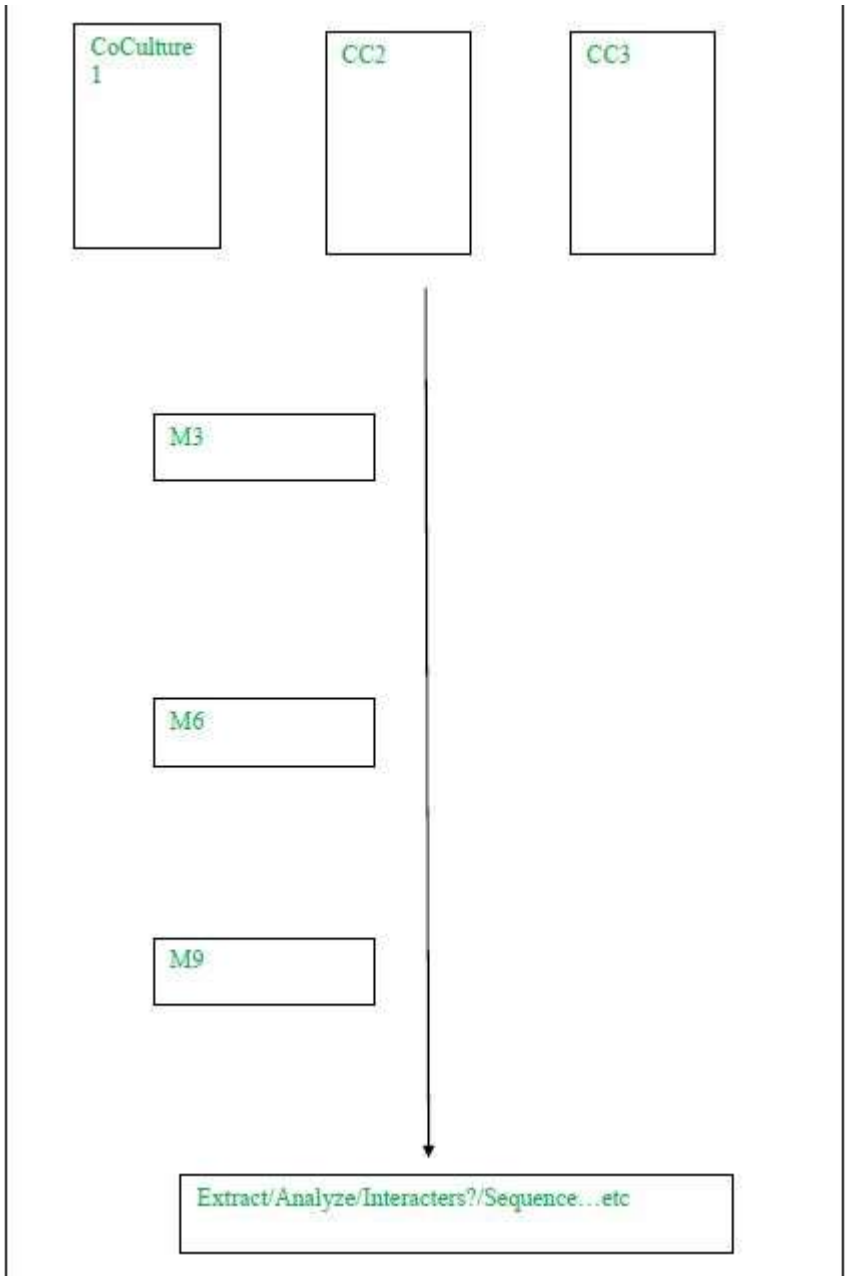

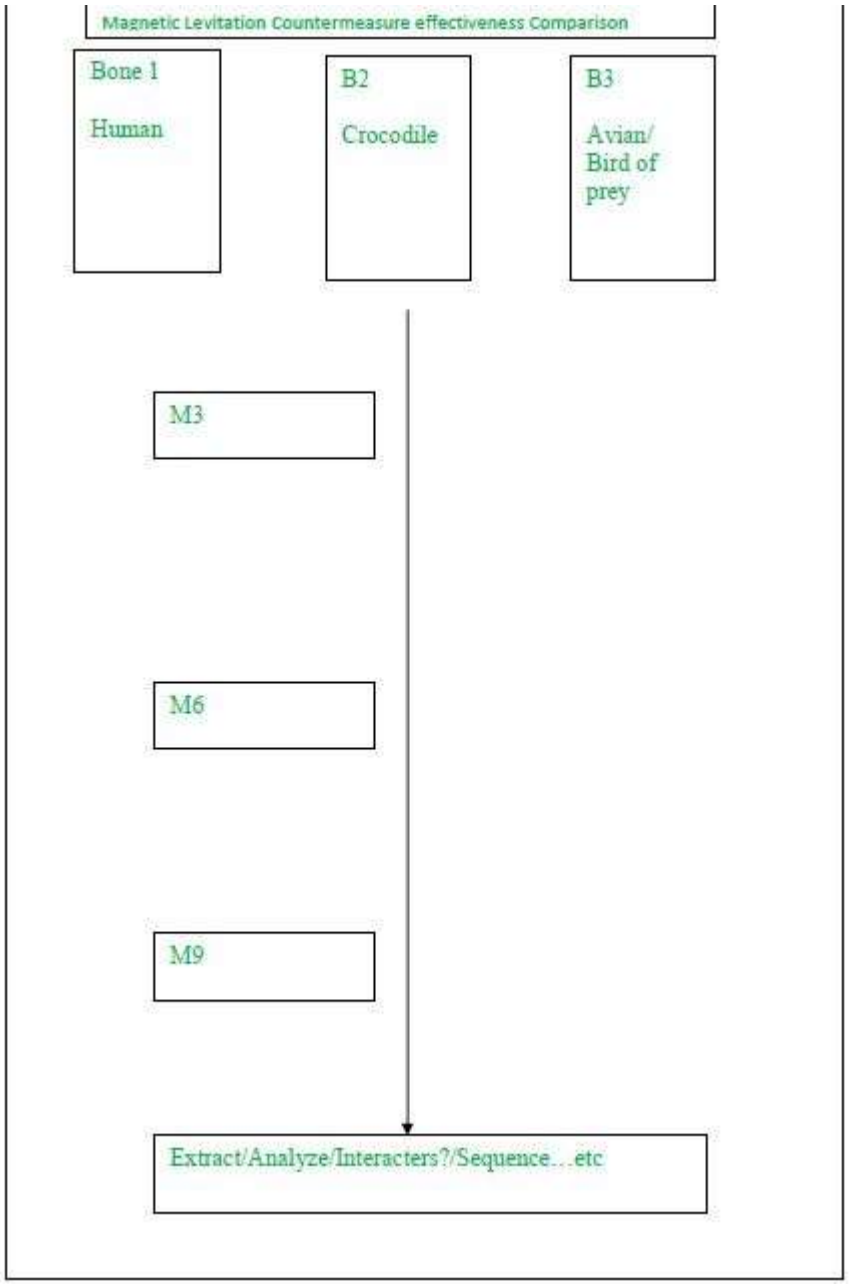
Magnetic Levitation Countermeasure effectiveness Comparison
Bone 1
Human
B2
Crocodile
B3
Avian/
Bird of
prey
M3
M6
M9
Extract/Analyze/Interacters?/Sequence…etc

**Supporting Information 4: Table 1. Global human population and predicted growth. Source: UNFPA, United Nations Population Fund estimate 31.10.2011.**

| Year | Population [Billion] |
|---|---|
| 1800 | 1 |
| 1927 | 2 |
| 1960 | 3 |
| 1974 | 4 |
| 1987 | 5 |
| 1999 | 6 |
| 2011* | 7 |

## 10. References


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