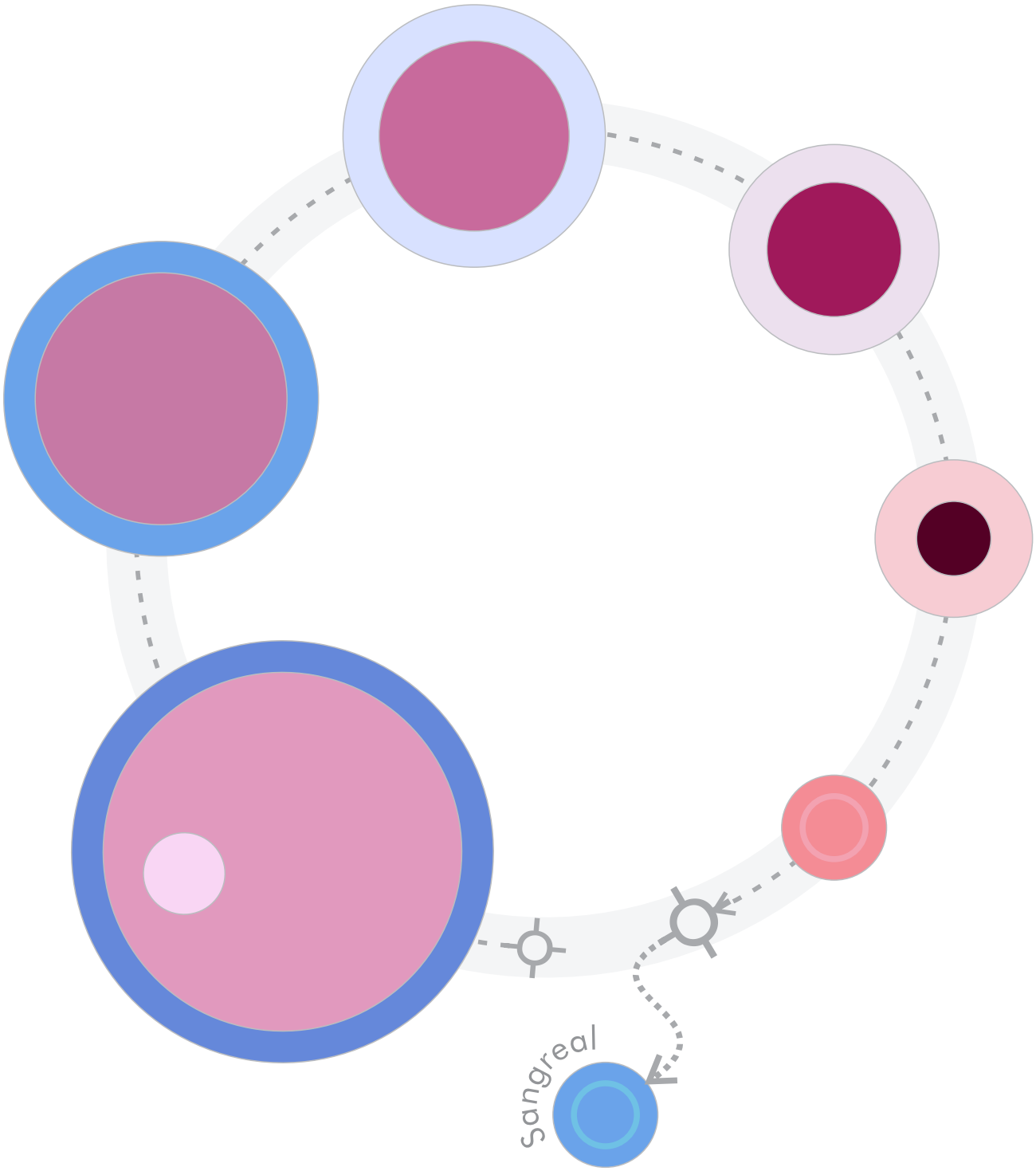


BIOMIMETIC
ERYTHROPOIESIS

Irena Pangeršič

IRENA PANGERŠIČ

BIOMIMETIC
ERYTHROPOIESIS

Kranj, 2016
Published by the author

CIP - Kataložni zapis o publikaciji
Narodna in univerzitetna knjižnica, Ljubljana

903(0.034.2)
2-264(0.034.2)
113/119(0.034.2)
612.119(0.034.2)

PANGERŠIČ, Irena
Biomimetic erythropoiesis [Elektronski vir] / Irena Pangeršič. - El. knjiga. - Kranj : samozal., 2016

Način dostopa (URL): http://gaja-upanje.herobo.com/download.pdf.php?file=Biomimetic-Erythropoiesis.pdf

ISBN 978-961-94075-1-6 (pdf)

286099456

Kolofon - Metapodatkovna oblika v Dublin Core

Atribut	Sistem	Podatki
DC.Naslov		Biomimetic Erythropoiesis
DC.Podnaslov		
DC.Avtor		Irena Pangeršič
DC.Avtor.Naslov		ariel.aneri@gmail.com
DC.Tema/Gesla		raziskave
DC.Tema/Gesla		Medicina
DC.Tema/Gesla		Arheologija; Arhitektura; Urbanizem
DC.Tema/Gesla		Zgodovina; Geografija
DC.Opis		Evolucija - Biomimetična razlaga razvoja človeške rase v paraleli z eritropoezo
DC.Založnik		Pangeršič, I.
DC.Založnik.Naslov		ariel.aneri@gmail.com
DC.Datum objave	ISO8601	30-03-2016
DC.Tip		Tekst/Teze/Raziskave
DC.Format	IMT	text/html&pdf format(višina 30 cm, širina 21 cm)/ teksti, fotografije, ilustracije, karte; 68 str.
DC.Identifikacija	PDF	Biomimetic-Erythropoiesis.pdf
DC.Identifikacija	CIP/NUK	
DC.Identifikacija	COBISS	
DC.Jezik	ISO639-1	angleški
DC.Dostop	URL	http://gaja-upanje.herobo.com/download.pdf.php?file=Biomimetic-Erythropoiesis.pdf
DC.Posodobitev	ISO8601	30-03-2016

Index

Space for Plato's Republic in The Seat of The Soul

Scientific research article

Space for Plato's Republic in The Seat of The Soul

all in reference to the *shape* of the all-seeing eye of God, a symbol of The Great Architect of the Universe

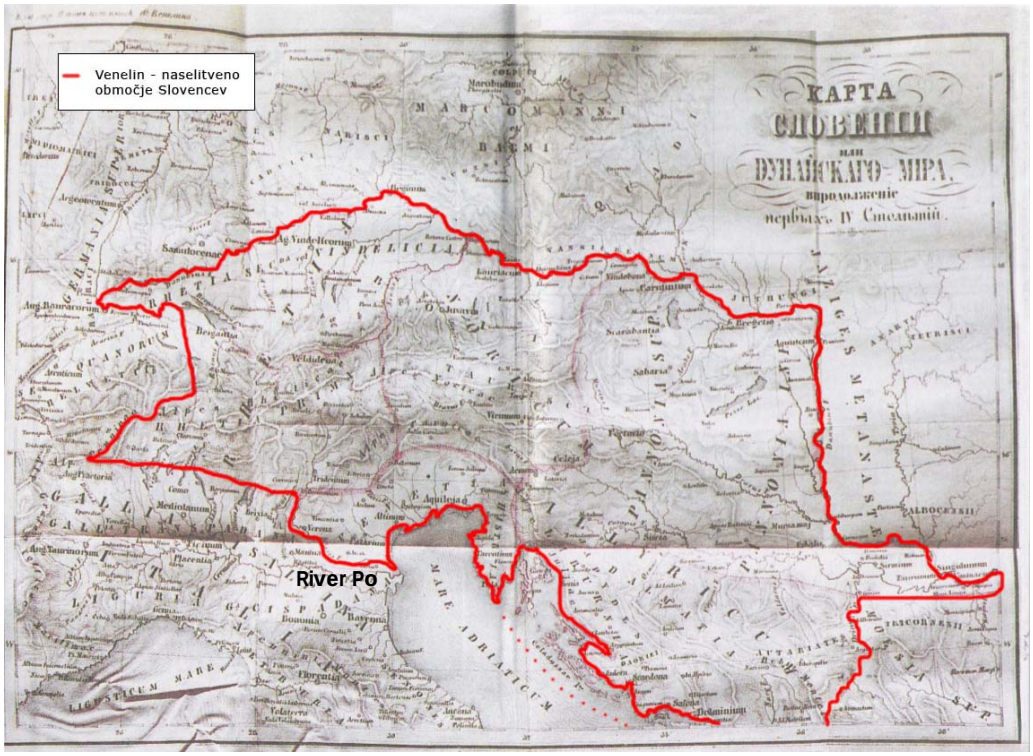
Irena Pangeršič
MA and BS in architecture, DipHE in Civil Engineering
e-mail: ariel.aneri@gmail.com

»Pherecydes of Syros once wrote that the Hyperboreans were a race of Titans and that Hyperborea was the birthplace of the first giants.«
H.P. Blavatsky [1]

Abstract.»Ancient Greek and Roman scholars mention a time when 'the Moon was not near the Earth'. Ancient records refer to people known as the Pelasgians, Proselenes, and the Arcadians. They were beings belonging to a very ancient race that inhabited our planet in times when there was no Moon. According to the Greek philosopher Aristotle, (384 BC - 322 BC), before the Hellenes occupied Arcadia, the land was inhabited by a group of people known as the Pelasgians. They 'occupied the land already before there was moon in the sky above the earth.' Plutarch, the Greek historian (46 - 127) confirmed this in his writings: 'There were Arcadians of Evander`s following, the so-called pre-Lunar people.' Also Ovid, a Roman poet (43 BC-17 AD) wrote of the pre-Lunar civilization. From his writings, we learn that 'the Arcadians are said to have possessed the land before the birth of Jove, and the folk is older than the Moon.' Apollonius of Rhodes who lived during the third century BC confirmed the presence of a very ancient pre-Lunar civilization in his writings. He wrote: 'when not all of the orbs were yet in the heavens, before the Danai and the Deukalion races came into existence, and only the Arcadians lived, of whom it is said that they dwelt on mountains and fed on acorns, before there was a moon.' Giordano Bruno, an Italian philosopher (1548 - 1600) was one of the earliest modern thinkers who contemplated on the existence of a pre-Lunar civilization. In one of his books he wrote: **'There are those who have believed that there was a certain time (as our mythology says) when the Moon, which was believed to be younger than the sun, was not yet created. The Arcadians, who dwelt not far from the Po, are believed to have been in existence before it (the moon).'**« Ellen Lloyd [2]

»The giants, in Slovenian called the Ajdi, are believed to be the oldest inhabitants of the Earth. The word Ajd has drawn attention up till now just for its possible indication of the archaeological sites. It is taken for a widely spread motif in folkloristics. The author includes the narratives about the continuity, cohabitation and appearance of the Ajdi from the prehistoric and Roman settlement on Ajdovščina above Rodik in the context of the specific area and time. The paper considers the possibilities of the historical truth of the studied oral tradition, which due to its uncommonness and connection to the specific place seems possible.« Katja Hrobat [3]

»Helmolts Weltgeschichte[4], notebooknr. 5, chapter »Das Auftreten der Kroaten und Serben«, page 277; »Es muss aber in Erinnerung gebracht werden, dass das ganze, jetzt von den Kroaten beseste und nach ihnen benannte Land früher den Slowenen gehörte und Slowenia hiess...« " and as stated by "Ožbalt Gutsman, Deutsch – windisches Wörterbuch [5], Celovec 1789, p. 284, explanation of the terms Slav – Slovenec, Slavenland – Slovenian land and Slavisch – Slovenian.«



Map from the ancient book 'Starodavni in današnji Slovenci' (Ancient and Modern Slovenians) /Jurij Venelin[1][6]*; [translaton from Russian by Ana Brvar, translation of Pavel Tulajev by Just Rugel, translation of Ovid from Latin by Barbara Šega-Čeh]. - Ljubljana : Amalietti & Amalietti, 2009 ([Ljubljana] : Schwarz) [pic.001]*

… and Arcadia was previously named Gigantis, land of the giants …[2]
Arcadia remained a beautiful, secluded area, and its inhabitants became proverbial as herdsmen leading simple pastoral unsophisticated yet happy lives, to the point that *Arcadia* may refer to some imaginary idyllic paradise, immortalized by Virgil's Eclogues, and later by Jacopo Sannazaro in his pastoral masterpiece, *Arcadia* (1504); see also Arcadia = utopia.[3]

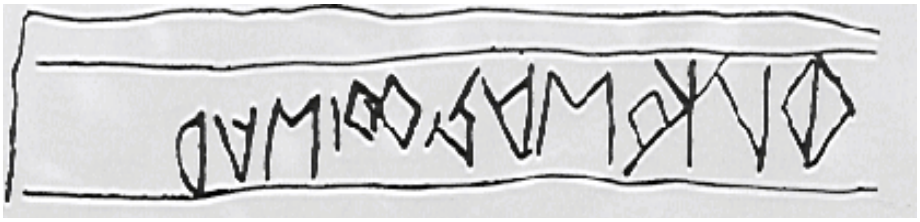
»A utopian land, known in our narrations as Koromandija, Komandija, Kolovozija, Kolobocija, Korotan, the ninth land, the paradise of loafers, Land of Cockaigne and also the "world upside down," and described also in both Slovenian legends about the Flood Myth, i.e. the time when we lost the utopian paradise twice because of reckless decisions and a disrespectful attitude towards nature.« Pangeršič Irena [7] [8]

"In ancient times there lived giants, the Ajdi. They had a human form, but they were extremely big. The first generation of the giants lived at 'Glassmountain', from where they moved to our highest mountains. If they wanted to talk with each other, they did not go to another village like we do, but they spoke while standing on the mountains. If one of them needed to borrow something from another one, he simply called and the desired object was thrown to him by his neighbour from the other mountain. They did not even go to fetch water with pots like we do, they simply leaned from the mountain and took the water from the river with a bucket … since they lived for a long time it could happen that the grandfather held his grandchildren's sons in his arms. The ancient generations of the Ajdi were sad when they realised the younger generation was not as largely built as they were. Finally, the youngest generation was born, and this is us, the people." Vinko Möderndorfer [9]

[1] *Venelin was born in 1802 in the Nagy-Tibava village (Velika Tibava) in the Carpathian mountains of Georgius Hutz. This was a Hungarian area, part of the then-Austrian Empire, which is now western Ukraine. The historian regarded himself as Carpatho-Russian. He took the last name Venelin (Venelovič) and the Russian name Jurij as an adult when he moved to Russia. Available at http://www.hervardi.com/jurij_venelin.php.*
[2] http://www.atlantida.gr/Eng/engAtlasArcadia.htm
[3] http://en.wikipedia.org/wiki/Arcadia

And the legend about the beginning of the world says that the Slovenians were, in ancient times when God still lived on earth, giants called Ajdi. The story also says that God, the creator, lived together with these people. However, he abandoned us because the people were afraid of him because of his mightiness and brightness.Kelemina Jakob [10]

In order to remember this and never forget that God went back to heaven, our ancestors carved this into stone and placed it solemnly in the place where God said goodbye to his people.



'BUG OŠA SO VIŠAD' [venetian]= 'Tu je Bog odšel v višave' [slovenian];
This is where God went to great heights;

A Venetian inscription [pic.002] from Würmlach [Bumlje in Slovenian], more than 2,500 years old, kept in the Provincial Museum of Carinthia in Klagenfurt.[11]

Even though the ethnogenesis of the Slovenians , according to the Venetian theory, stems from the basis that they were as much Paphlagonian and Adriatic as they were Baltic, and ancient Armorican inhabitants called Eneti , Veneti , Venedi, or Vends were actually predecessors of the Slavs Robert Petrič [12] it is forgotten that people on earth only spoke one human language in ancient times, until the collapse of the Tower of Babel. And according to the records: »Abu 'Isa, the astronomer quoted by Abu al-Fida [13][»Historia Anteislamica«, ed. Fleischer, p. 18 in 19] [14], also tells the Biblical story of the Tower and the confusion« - he adds that only Eber's[4] people were able to maintain the original language of humanity because they did not participate in the construction of the Tower of Babel. [*However, Biblical scholars have discovered that Eber*[5] *also means "away" or "outside," out of the region or across, the opposite side, or "the ones who went away."*]

The giant Nimrod building the Tower of Babel[6]*[pic.003]*

[4] *Eber - lingua humana [Latin]= »the human language« →according to Hebrew testimony*
[5]http://www.jewishencyclopedia.com/articles/7445-hebrew
[6]*Salerno ivory, 11th cent.* http://www.tali-virtualmidrash.org.il/ArticleEng.aspx?art=28

... and the composition of the town of Babylon with the Tower of Babel
was shaped in the form of the "all-seeing eye", as an idea to enable
King Nimrod to carefully follow the happenings on earth
from his temple in heaven...[7]

However, Pseudo-Philo VI. 5-18 [15] also quotes Abraham from this period, as well as eleven other men who opposed the construction of the Tower of Babel and thus were the only ones spared when God descended on earth, and the tower collapsed and burned down: »According to this Midrashic account, Abram with eleven other men whose names are given, refused to bake bricks for the building of the Tower of Babel. In consequence, they were seized by the people of the land, and brought before the princes, and on their persistent refusal to take any part in the building of the Tower, were condemned to be burnt. A respite of seven days is given them at the intercession of Jectan, "the first prince of the captains," but at the end of th is time, if they have not already changed their mind, they are to be handed over for execution. Jectan, a secret friend, contrives their escape to the mountains, and eleven of the men do escape, but Abram refuses to flee, and remains behind. At the end of the seven days, the "people of the land" demand that the imprisoned men shall be produced. Jectan explains that eleven of them "have broken prison and fled by night," but Abram is produced, is cast into the fire, but is miraculously delivered by God,[8] who causes an earthquake which breaks up the furnace and scatters the fire, which "consumed all them that stood round about in the sight of the furnace; and all they that were burned in that day were 83,500. But upon Abram was there not any the least hurt by the burning of the fire.«

The Tower of Babel[9] *[pic.004]*

And despite the long forgotten time of the construction of the Tower of Babel, when we as the only people were spared [by being able to keep the original language of humanity], here the only remaining memory of these times is the inscription on the beehive panel [pic.005] kept in the Slovenian Ethnograhic Museum630:LJU;0007288[16] and named in the inscription as: The Tower of Babel". : Inv. n. 7288; 13 x 28 cm; upper left corner number 8, and right corner number 88; the beehive panel was found at "Andrejčnik" in Gornji Grad in the Savinjska Dolina.

[7]Available on August 22, 2012 at: http://christianitybeliefs.org/thefuelproject/the-tower-of-babel-heaven/
[8]*According to R. Eliezer b. Jacob it was Michael who delivered Abraham from the fire; but the prevailing view was that it was God Himself; cf. Bereshith rabba xliv. 16.*
[9] *Available on August 25,2012 at* https://sites.google.com/site/crossbr/babel.jpg

The beehive panel [pic.005]

The Tower of Babel = Bab-el[10] … the Gate of God;
and Ezra[11] states in his records 8_88:

88 You were so angry at us before, that you could have destroyed as all!89 You didn't, though – you were faithful and allowed some of us to survive. 90 But now we admit that we have sinned and are not fit to worship you.

The brave decision of twelve men to no longer participate in the construction [considering that at first the purpose of the tower's construction was to build a structure to worship and honour God – later the builders decided that the tower would be used by priests, because of their haughtiness, so that they could reproach God the creator for his creation] could be compared with the unique law of the Slovenian people [Lawof the Twelve], preserved until the French occupation of our regions [1797, 1805-06, 1809-13], when they cut down all of the lime trees [the Slovenian tree of life] where this legal order had been preserved for centuries – i.e. the so-called "dvanajstija" or "the dozen."[12] And the Slovenians, more out of mockery than out of honour, still say about themselves when talking about their decisions that they are "more papal than the Pope himself".

With the cutting down of numerous lime trees, not only has Slovenian law died out, but also the so-called peak of people's joy, dancing under the lime, called "the dance under the lime" or "the high dance" or "the first paradise dance".

The lime tree appears as a holy tree in the tradition of all the ancient Slavs, but only in the Slovenian tradition is it respected as the tree of life. The 'typical' lime leaves that do not fade on the tree of life and represent health for the people appear in the tuft of feathers on helmets [seal of the marshal of Styria, 1278]. Šavli [17]. According to common belief the lime tree has magical properties because it protects from lightning, various accidents, diseases, evil spirits and witchcraft.

Pliny[13] the Elder mentions that the lime tree leaves help against a thousand cases of illness, while the lime tree wood does not get eaten by worms. Above all, the abundant lime

---

[10] *Hebrew: bab-el, from bab "gate" + el "god" - Is it called* gate of God *because here God "came down" 22.8.2012 on:* http://www.emergingtruths.com/tower_of_babel/tower_of_babel.html

[11] *The name Ezra means "God helps" and his book [regarded by Christianity as apocrypha in some records = i.e. a forged paper] speaks mostly about the departure from Babel and the reconstruction of the eternal city.*

[12] *Rallies and legal actions took place under the lime trees; historic sources describe this as "institution sclavenica" (Slovenian law) and "consuetudo sclavorum" (Slovenian habit) – in Slovenian regions this task was assigned to the mayor and his "dozen," comprised of twelve men who were at the head of the village community. These assemblies under the lime trees were preserved until the 16th Century [and ended with the peasants' revolt], while the mayors with their "dozens" lasted even until 1848; Even the most heated disputes between neighbours were solved under the lime trees. Unfortunately, a large number of lime trees were cut down during the French occupation, because the Slovenian legal order was not consistent with the French constitution. Šavli J.* [17]

[13] *BOOK 24: CHAP. 34. THE LINDEN-TREE I FIVE REMEDIES.*

tree inflorescence is excellent and the most rich honey chamber. The Book of Revelation [22, 1 and 2] foretells that the tree of life will be a reward to the righteous for their good works at the end of the world. Quote: 1 And he shewed me a pure river of water of life, clear as crystal, proceeding out of the throne of God and of the Lamb. 2 In the midst of the street of it, and on either side of the river, was there the tree of life, which bare twelve manner of fruits, and yielded her fruit every month: **and the leaves of the tree were for the healing of the nations.**The Holy Bible: King James Version[18]

Construction ofthe tower of Babel."The construction of the high tower progressed gradually. Years had to pass for the ground floor to be completed. Because of the extent of the construction, the area appeared low, not at all grand, resembling more of a sheep barn than a house of God. Some priests already loudly expressed their doubts about the tower ever reaching the 'sky.'"... "The links between individual sites were gradually but completely interrupted. Everyone shaped his own way of life and customs. Years passed, priests died, their successors only accepted their heritage with lenient understanding and dreamed about their own great deeds. They simply did not believe that it could be possible to build a sky-high tower, since they already knew something about the sky, but they still believed they would be able to inhabit these towers." ...And in the land of Shinar, after God had come down from heaven and confused their languages, many different kingdoms were created ... "The priests claimed that the communityof people who did not build the tower, are to be blamed for the failure. Should we agree with them? It is known that these people continued visiting that place still for many centuries after that and admiring the great deed of their ancestors. Anyway. A place remained that was intended to become a stairway to the sky, but it only remained a symbol of confusion." Vladimir Kavčič [19[14]]

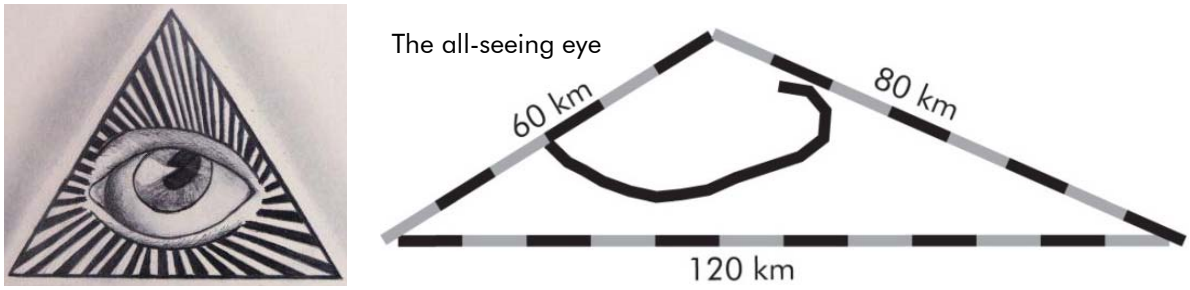
Satellite archaeology in the area where the Venetians worshiped the place of God's departure back to heaven [A=Würmlach] shows a large triangular formation [pic.006] with a central, partially oval part [https://maps.google.si/maps?hl=sl]

The linden-tree is useful, thougli in a less marked degree, for nearly all the same purposes as the wild olive. The leaves, however, are the only part that is made use of for ulcers upon infants ; chewed, too, or employed in the form of a decoction, they are diuretic. Used as a liniment they arrest menstruation when in excess, and an infusion of them, taken in drink, carries off superfluous blood. [20]

[14]PROBLEMI: magazine for culture and social issues – Year 1, n. 1 (1962) – Ljubljana: Society for theoretical psychoanalysis, 1962- . -24 cm.

Satelite magnification ofone of theanglesofa gianttriangle [pic.007]

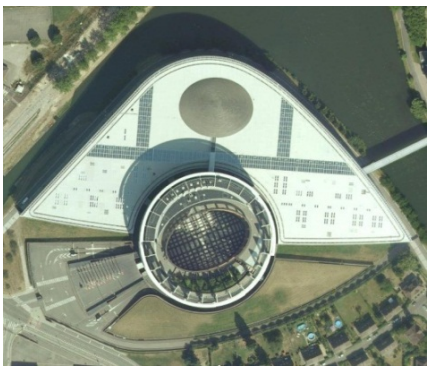
Even detailed enlargements in the western part of these triangular formation show the shape is correct but unfortunately collapsed [triangular formation = town, and oval formation = parts of the tower][pic.006]. Satellite archaeology also reveals that a huge triangular formation[15] really does represent the shape of the "all-seeing eye of God" [pic.008, 009] which was once worshipped by the Egyptian community, while today it is known in Hinduism as the third eye of the god Shiva, worshipped in Christianity as the Holy Trinity, and representing the "Eye of Divine Providence" in freemason societies – which actually represents the seat of the soul and whose first worshipper was Nimrod himself – a great man and hunter before God [adapted from Bible 1 Mz 10,8-10,9 and Ch 1,10] [21].



Above [Pic.008 in 009]

»And they said: come, let us build us a city, and a tower (11:4)« … »A third of this tower which they built sank [into the earth], a third was burnt, while a third is still standing. And should you think that it [the remaining third] is small — R. Huna said in R. Idi`s name: When one ascends to the top, he sees the trees below him like grasshoppers.«Midrash Rabbah [22] –'even after there was only one third left and the trees below still looked like grasshoppers'.

[15]*Giovanni Villani (1300)*[23]*: He relates that "it measured eighty miles round [129 km], and it was already 4,000 paces high (5,920 m (19,423 ft)) and 1,000 paces thick, and each pace is three of our feet." [14]. Tower and wall of Babylon was began 700 years after the Flood or 2364 years from begining of the world.*




The City and the Tower of Babel - The European Parliament [pic.010, 011]

As a curiosity: the recomposition of the Tower of Babel represented by the EU Parliament building complex literally recreates all key elements of the archaeological remains of satellite archaeology: the triangular eye shape = the main building, dome shape = the eyeball, the unfinished shape of the entrance hall = the portal where God left Earth.

The ancient people – Venetians, who went on a pilgrimage after the collapse of the Tower to the town of Bumlje where God had left them – can be paralleled with the Samoyedic people from Ural who call their language Yenetic [as Slovenian and Venetian, also the Yenetic language knows the dual form, which is basically only found in one other language – the Sanskrit].

Today,few world languages use the grammatical dual. Among those that can boast this language characteristic are allSamoyedlanguages as well asSlovenian,whichdeveloped from theVenetianlanguage. Researchshows that Slovenian is theoldest proto-languagein Europe. However, thedualis not the onlycommon featureof the Slovenian andSamoyedpeoples. They also share afeaturecalled GIANTS, who had supposedly lived on earth[fairy tales, legends, the Bible, Siudbabts[16]– the heroic epics of the Nenets about the giantsandEneoh's records[17]]. The legend goes that the original 12giantslivedonCrystalMountain, from where theymoved to the Slovenianmountainsandsettled[24].

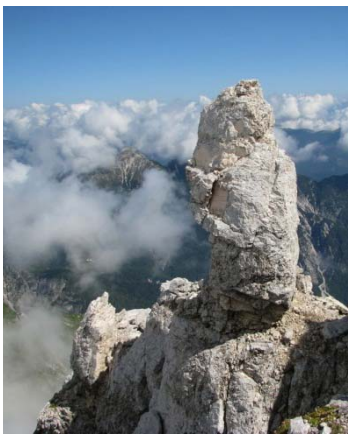
Enormousforms, suggestingthearchaeologicalbuilding remains of giganticproportions, are represented at 'Špik nad Policami'[Jôf di Montasio in Italian or 'Montaž' in Slovenian], which is located in theVenetian Alps [now known as the Julian Alps].


Little 'Sphinx' or 'big pussy-cat'[pic.012] [height of approximately7 m and length ofapproximately10 m] anda big 'Window'[pic.013], both on the mountains of 'Špik nad Policami'

[16]http://www.everyculture.com/wc/Norway-to-Russia/Nentsy.html

[17]*Noah'sgreat grandfather, whoserecordsareonlyrecognized by the EthiopianandEritreanOrthodoxCommunities, accessedon25 August 2012at*
http://en.wikipedia.org/wiki/Book_of_Enoch

'Double Window' [pic.014]and the presentation of the size of a managainst thehugebrick rocks [each stratum is approximately3-7 m high] – named 'Lego bricks'[18]*[pic.015] by the author[Primož Blaha] of the photo. Both on the mountainsof 'Špik nad Policami'*



Megalitsontop of a mountainŠpik are overlookingthe valleybelow all on the mountains of 'Špik nad Policami'[pic.016,017,018]

Demolished megalithictempleMetulum [formertemple ofthe sun]and enormous 'snake head'[19][25]*stone foundalso under the mountainŠpik by Dimitrij Kebe*[20]*and his relative in August 1999 [pic.019,020]*

[18] *Primož Blaha at* http://primozblaha.wordpress.com/2011/10/03/poliski-spiki-1-10-2-10-2011/ *and Špikomanija at* http://www.gore-ljudje.net/novosti/57683/

[19]*Stone caled 'Snake head' [in Slovenia] or 'snake egg' [in Britain] or 'chicken god' [in Russia]. Such stones have been discovered by archaeologists in Britain, Egypt and Slovenia. Stones were believed to have magical powers such as protection against eye diseases or evil charms, preventing nightmares, curing whooping cough, the ability to see through fairy or witch disguises and traps if looked at through the middle of the stone, and of course recovery from*

Enormous'tables' or 'mushrooms,' asthey were known by the localsin theSloveniankarst region, are also theremnantsofthe ancient,heroictimes whenthe firstgenerationsof giants lived. [pic.021,022]

Theyhave been preserved up to the present time. Stone mushroom[Left pic. 021] and Tomaž's Table[Right pic. 022].

King Matthias, mighty giganticHyperborean [Arcadian] king.The version of the tales about King Matthias, who sleeps in Peca, deriving from the Lower Carniola (Dolenjska), talks about the mighty gigantic pagan king (*Ajdovski kralj* in Slovene) [27], who provokedaconflictwith God –KingMatthias, the ruler of Slovenians [28]… and 'every hundred yearsthe goldenbirdflies to Sveta Gora[Mount PecaorKordež's Head] andsings a song. King Matthias wakes up, looksaround the world,and goes backto sleep.However, when times will be the worst, thegoldenbird will sing so sadly that Sveta Gora will open and King Matthias andhiswarriorswillwake up andkill all the tyrants. And again justice will rulethe earth'. Do you know whoKing Matthias is? This is a Sloveniansoulwho, together with his knights, sleeps in the mountain for centuries because they were captured by the enemies of the Slovenian nation-adapted fromMalovrh, MiroslavKralj Matjaž [29]

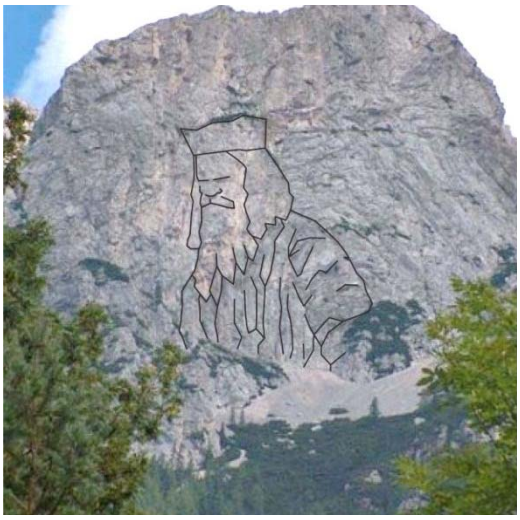
King Matthiasand his knights on a beehive panel, above [pic.023]

According to legend, King Matthias sleeps with his knights[21] in the cave on Mount Peca andwhen hisbeard will grownine timesaround thestonetable they will all wake upand take the human raceonce againto the Golden Age.

snakebite. According to popular conception, a true adder stone will float in water. The stone can be any rock with a hole bored through the middle by water. Human intervention is not allowed. [26]

[20] *Magazin Misteriji september 2011 on:* http://www.misteriji.si/art/Letnik_2011/Misteriji_218

[21]http://www.akropola.org/App_Upload/Image/galerije/slike/PR_SLO_Kralj-Matjaz-%20big.jpg




Has King Matthiaswoken up? … King Matthias, the rulerof the Golden Age who has stirred the imagination of Slovenians for centuries, indeed showed up on Mount Peca in 2006[22]– the shape isvisible fromTopla DolinaValley[23]near 'Črna na Koroškem'[24]. [pic.024,025]

In Greek mythology, is the rulerof mankindin theGolden Age ofTitan,Cronus, who ruled the earth along with the otherelevenTitans. The establishment of the newGolden Age of Kronos, a timeof peace and justice,"when a new generation of humanity is supposed to have comedown from heavento the earth," is also described by the poetVirgilin the fourthEclogue[25]. [30]

Now the last age by Cumae's Sibyl sung
Has come and gone, and the majestic roll
Of circling centuries begins anew:
Astraea[26] returns,
Returns old Saturn's[27] reign,
With a new breed of men sent down from heaven.

In the foreword to a collection of"VolksliederausKrain" (Leipzig 1850,p. X), AnastasiusGrünwrote thatKing Matthias was "ein fastfabelhaftesWesen" (an almost fabulous creature). In a text written by Peterlin from Lower Carniola – Grafenauer No. 41 –King Matthiasisa kind ofgiant, three times bigger than the biggest among the currently living human beings and a modern man does not drinkeven a half of the measure that was three times a day drunk by the smallest subject of King Matthias. King Matthias considers the people who currently live on the Earth nothing more than weaklings, whom he will get rid of when he wakes up.This is where the traditionof the weakening human race derives from (cf. Št. Kuhar, Kakši so bili lidjé prad nŕmi pa kakši do za nŕmi? ČZN VIII, 1911. 61) [31]

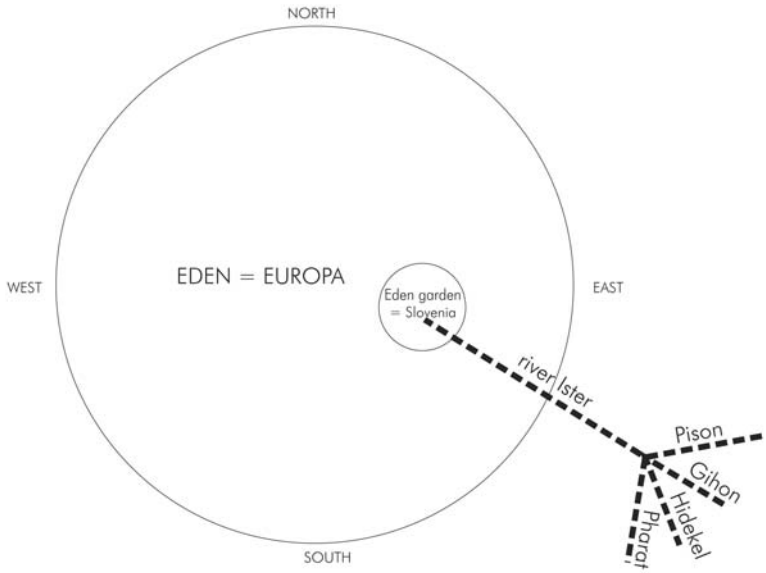
King Matthias–IX. Written down by Rok D[rofenik] Gorski in the areaaroundPtujska gora. VrtecXVII, 1887, No. 12.213-214(hereinafter the publications and reprints of Vrtec from 1884– therefore No. IX) Varianta h Graph. t. 23-37, »Obisk pri Kralju Matjažu« - 'Visit at King Matthias'; prim. Graph. t. 41 and 42. Contents: the missionary who is sentenced to death (!) is promised to be released, if he goes to the kingdom of King Matthias and inquires about the Judgment Day. On the way there he takes a nap, just for "a few hours" =300 years. When he

[22] *Accessed 22 Aug. 2012 at* https://24ur.com/ekskluziv/zanimivosti/kralj-matjaz-na-peci.html?ar=
[23]*Topla istheAlpine valley below the southern walls of Peca near Črna na Koroškem. Being one of themost beautiful and interestingSlovenianvalleys, thearea, which covers about1350hectares, has been protectedsince 1966 as a natural parkand a natural monument. Through the valley, Topla stream runs, which flows into Meža River.*
[24]*On 8 January 2006, Slovenian songwriter Milan PečovnikPiđi discovered the face of King Matthias in the rocksofMt Peca*
[25]*The Eclogues also called the Bucolics, is the first of the three major works of the Latin poetVirgil.*
[26] *Alias Justitia – Personification of justice*
[27] *Cronus*

arrives to King Matthias, he tries to pull the sword from thescabbardandlearns that theJudgment Day will come when the"sword will jump from the scabbard alone." After returninghome, the missionarydoes not dieimmediately.[31]

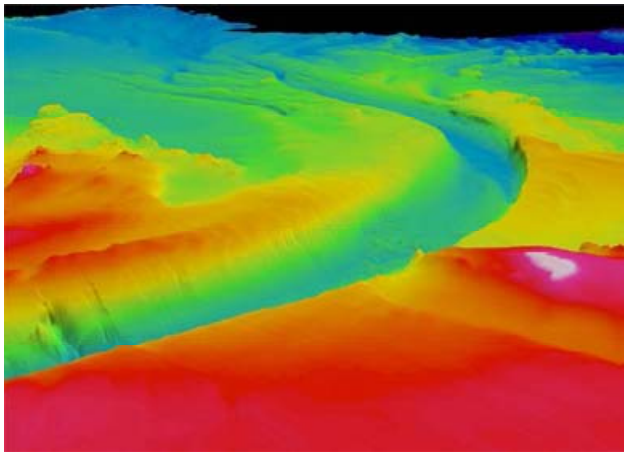
Ancient famous Paradiseriver Ister.According to Herodotus [4th book, chapters 48, 49] [32] the Eden River called Ister [river called after goddess Ishtar], which was still known in the Silver Age, was the most prominent river in the Old World and following its passage into the present area of the Black Sea it ramified. While in Herodotus' time it had a five-branch river mouth, it currently has only a three-branch one [and an artificial river bed]; in the period before the Flood it probably had a four-branch mouth [pic.028,029].

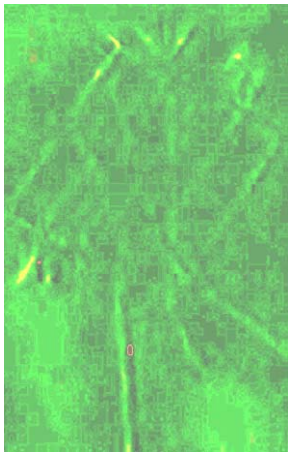
Goddess Ishtar and all-seeing eye [pic.026]; Holy Lady on the ancient cathedral of Carantania, the first Slovenian state – 'Gosposvetsko polje', Gospa Sveta (german:Maria Saal) [pic.027]; Below: Reconstruction of the Garden of Eden according to the record in the Bible [pic.028]



Ister, also known as Savus, on Abraham Ortelius' map from 1624[33] *[pic.029]. Easter/Ister is the second name for Ishtar or Astarte, "the Queen of Heaven or Eden Queen."*[28]

The changes on the earth's surface in the area of the Black Sea were major after the Flood [pic.030,031]. As William Ryan and Walter Pitman from Columbia University established in 1997, the common theory of the formation of the Black Sea indicates that a massive amount of water flowed through the Bosphorus Strait [present Istanbul], where the water from the Mediterranean flooded and filled a smaller freshwater lake.



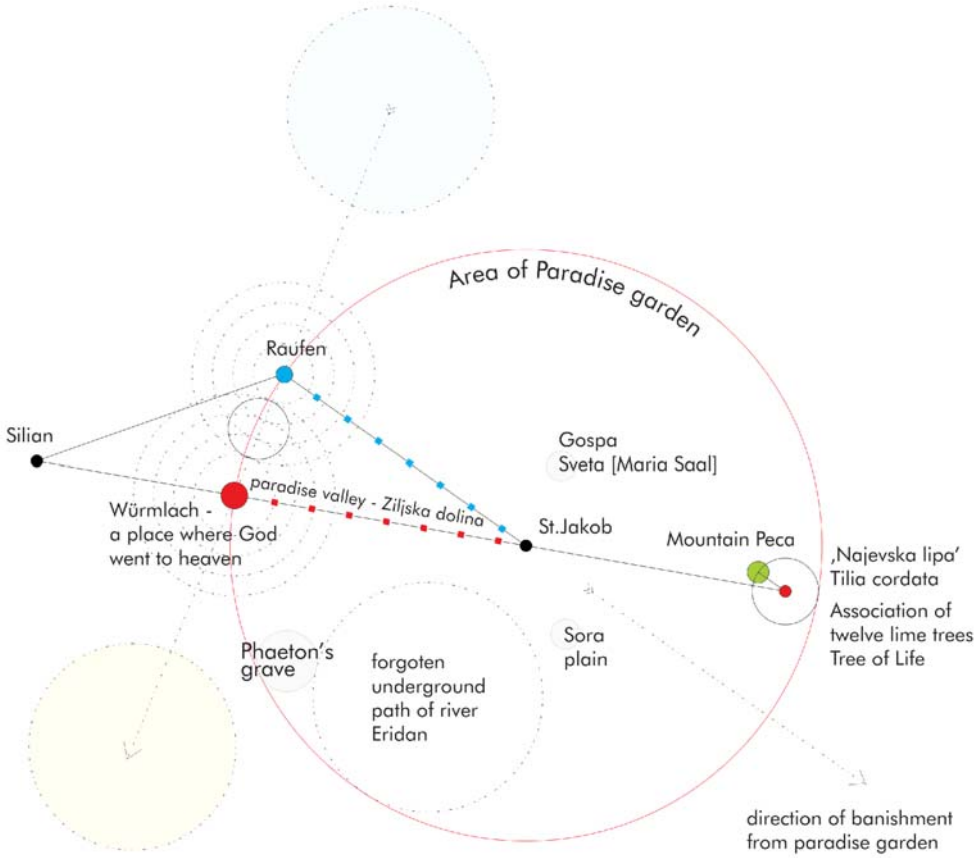


The deep bed of the former river under the Black Sea from the Mediterranean through the Bosphorus [pic.030] and part of the structure of large settlements under the Black Sea [pic.031]

This catastrophe irreversibly changed the history of the people living in this area, as well as the life of animals and plants. According to the theory, before that date the glacial melt water that

[28] *"8 And the LORD God planted a garden eastward in Eden; and there he put the man whom he had formed. 9 And out of the ground made the LORD God to grow every tree that is pleasant to the sight, and good for food; the tree of life also in the midst of the garden, and the tree of knowledge of good and evil. 10 And a river went out of Eden to water the garden; and from thence it was parted, and became into four heads. 11 The name of the first is Pison: that is it which compasseth the whole land of Hav'ilah, where there is gold; 12 and the gold of that land is good: there is bdellium and the onyx stone.13 And the name of the second river is Gihon: the same is it that compasseth the whole land of Ethiopia. 14 And the name of the third river is Hid'dekel: that is it which goeth toward the east of Assyria. And the fourth river is Euphra'tes." The Holy Bible*[21]

once supplied the coasts of the Black and Caspian Sea, and the freshwater lakesthat occupied vast areas, emptied into the Aegean Sea. As the glaciers retreated, the water level was reduced [...][29]William Ryan and Walter Pitman [34]. Yet the colossal changes led also to the loss of any trace of the four rivers that once flowed from Eden.



Gospel of Thomas, 18 [35]
.. For where the beginning is, there will the end be ..

Reconstruction of the Garden of Eden according toKing Nimrod's regional planing of Tower of Babel in shape of the all-seeing eye of God[pic.033]

Conclusion. In Greek mythology the soul represents the beginning of life and the beginning of living nature. For Anaxagoras it represents the cause of movement, Thales adds counter pole nature with movement, while according to Aristotle the theory of the soul is in the metaphysics[30] of the living world, the highest level of which is the human being. *Kalan, Valentin* [36] Man's creation according to the Bible places him into Eden, which existed in a material way, considering that it is described as the area of four rivers that watered the garden – the Pishon, the Gihon, the Hiddekel and the Perath. Among other things, there are also the tree of life and the tree of knowledge of good and evil growing in the Garden of Eden, standing in opposition – the usefulness of each is to be judged by the human, who is not aware of the consequences that await him. *Krause, J.E. and Terrien, S.* [37] As a means of global arbitration and just action of the human, according to ancient Egyptian beliefs, it

[29] *Accessible on 30 May 2012 at:* http://sofiaecho.com/2011/07/07/1119372_archaeology-black-seas-ancient-coast-found-report
[30] *a philosophy that deals with the principles of reality which are inaccessible and unrecognisable to emotions*

represents the eye of "Udjat"[31], which lives its own life and represents the symbol of the soul's wisdom. In Hinduism the nucleus of the soul was represented by a third eye [the seat of the sixth chakra], the main organ of which is the hypophysis, which is functionally divided into adenohypophysis and neurohypophysis; in an anatomical sense it is divided into the anterior lobe, the middle lobe and the posterior lobe. *Štiblar-Martinčič, D.*[38].

Democritus claimed that the soul is some kind of fire and warmth [Aristotle in Kalan, V.][36] that is the beginning of life, also described as the oldest belief in the soul in the form of a bird in the myth about Phoenix, the purple firebird made of the force of life which represented the soul in the Egyptian world. The two-headed Phoenix, however, as the androgynous freemason symbol of the 32nd and/or 33rd level represents the royal memorial and the messiah from whom the salvation of the world depends on, and whose mission, symbolised by the old coat of arms, is also attributed to the Province of Carniola. [pic.033]

The two-headed blue and golden Phoenix on the coat of arms of the Province of Carniola and the one-headed red and golden Phoenix on the coat of arms of Kranj in the code: "The Kranj Antiphonary"[32] writer and illuminator Ioannes von Werd de Augusta, August 17, 1491.[39] *[pic.033]*

New Golden Age.A folk tale says that he there shall be a decisive battle at the Sora plain [field near Kranj] in which seven kings shall compete. A "spruce with seven peaks" sprungat the Sora plain, causing the beginning of harsh times. Seven largearmies come to the plain, where it is decided who shall be the lord of the world.

The war is ended with the signing of a peace treaty by theseven kings under the storm-weathered three [with seven tops] [40], after which the Golden Age follows. [41] According to the folk song, the marvellous rays of a Golden Age shall glow from the sky and calm the whole world. Different nations shall celebrate together, everyone shall be their own lord, and the most beautiful day shall come for the Slovenian nation. [41]

Translated by Brina Beškovnik Hrastar, University graduate in translation

[31] *the eye of Horus (originally the eye of Ra) is the symbol of indestructible royal power. The eye is comprised of six shapes, which match the six senses : touch, taste, hearing, thought, sight and smell. Horus was the ancient Egyptian god of the sky; one of his eyes was the sun , the other one was the moon. Ra (also Raa) in ancient Egyptian mythology is the god of the sun, the creator of people and gods. He is the highest god in ancient Egypt.*

[32] *book of choral songs, sung in turn by two choirs or by a solo singer and a choir*

Bibliography:

[1] The secret doctrine; The synthesis of science, religion, and philosophy; H.P. Blavatsky, 1888

[2] Voices from Legendary Times: We are a bridge between past and future, Ellen Lloyd, 2005, iUniverse, Inc.

[3] Katja Hrobat: Ajdi from Ajdovščina above Rodik, Studia mythologica Slavica VIII, 2005, str.99-112

[4] Weltgeschichte/begründet von Hans F. Helmolt ; herausgegeben von Armin Tille. - 2., neubearbeitete und vermehrte Aufl., Neudruck. - Leipzig : Bibliographisches Institut, 1923-1924

[5] Deutsch-windisches Wörterbuch mit einer Sammlung der verdeutschten windischen Stammwörter, und einiger vorzüglichern abstammenden Wörter / von Oswald Gutsmann ; auf Slowenisch-Deutsch umgekehrt und bearbeitet von Ludwig Karničar. - Graz : Institut für Slawistik der Universität, 1999 (Graz : Styria).

[6] Starodavni in današnji Slovenci / Jurij Venelin ; [prevod iz ruščine Ana Brvar, prevod Pavla Tulajeva Just Rugel, prevod Ovida iz latinščine Barbara Šega-Čeh]. - Ljubljana : Amalietti & Amalietti, 2009 ([Ljubljana] : Schwarz). - 333 str. : ilustr. ; 24 cm. - (Zbirka Razgaljanje zamolčane zgodovine)

[7] Pangeršič, Irena: Feniksova skrivnost konglomeratnega krasa. Gorenjski konglomeratni kras [Elektronski vir] / El. knjiga. - [Kranj] : [samozal.] I. Pangeršič, 2011

[8] Pangeršič, Irena: Vindija Koromandija [Elektronski vir] : dežela za devetimi gorami in devetimi vodami / El. knjiga. - [Kranj] : [samozal.] I. Pangeršič, 2011

[9] Koroške narodne pripovedke/ selected by Vinko Möderndorfer ; illustrations by Franjo Stiplovšek. – In Celje : Družba Sv. Mohorja, 1937

[10] Kelemina, Jakob: Bajke in pripovedke Slovenskega ljudstva, Humar, 1997

[11] Provincial Museum of Carinthia, Museumsgasse 2, A-9021 Klagenfurt, Austria

[12] Robert Petrič: Venetska teorija in izvor Slovenov, Proceedings of the Fifth International Topical Conference ORIGIN OF EUROPEANS, uredil Anton Perdih. - Ljubljana: Jutro, 2007

[13] The Concise History of Humanity or Chronicles (Arabic: 'Tarikhu 'al-Mukhtasar fi Akhbar al-Bashar المختصر في أخبار البشر'), or Tarikh Abi al-Fida تاريخ أبى الفداء (History of Abu al-Fida), is a history book authored by Abu al-Fida Ismail Ibn Hamwi in 1315 and continued by the author to 1329. (Constantinople, 2 vols. 1869).

[14] Abū al-Fidāʾ Ismāʿīl ibn ʿAlī, 1273-1331: Historia anteislamica, arabice e duobus codicibus Bibliothecae regiae Parisiensis, 101 et 615 / Abulfedae ; edidit, versione latina, notis et indicibus auxit Henricus Orthobius Fleischer. [Mukhtaṣar fī akhbār al-bashar. Latin & Arabic] Arabic and Latin on facing pages. Includes indexes. Lipsiae : Vogel, 1831.

[15] The Biblical Antiquities of Philo [Pseudo-Philo], Edited for the first time in English by Dr. M. R. James, and published in this Series

[16] Slovenski etnografski muzej, Metelkova 2, SI - 1000 Ljubljana, Slovenija

[17] Šavli, Jožko: Slovenska znamenja / Bilje : Studio Ro, Založništvo Humar, 1994

[18] Holy Bible, King James Version Published December 1999 by American Bible Society

[19] Vladimir Kavčič: Stolp v Babilonu, 1962: Problemi št.1, revija za kulturo in družbena vprašanja

[20] Pliny, the Elder; Bostock, John, 1773-1846; Riley, Henry T. (Henry Thomas), 1816-1878 Volume: 5, Subject: Natural history -- Pre-Linnean works Publisher: London, H. G. Bohn Year: 1856

[21] The HOLY Bible [1981]: containing the Old and New Testaments : revised standard version / translated from the original tongues being the version set forth a.d. 1611 revised a.d. 1881-1885 and a.d. 1901 compared with the most ancient authorities and revised a.d. 1951, 2nd ed. of the New Testament a.d. 1971. - Oxford [etc.] : Oxford University Press, [1981] Ljubljana : Mladinska knjiga

[22] Midrash Rabbah. 1, Genesis I / translated by H. Freedman. - 3rd edit. - London ; New York : Soncino press, 1983. – XXIX]

[23] The Chronicle Of Villani, Translated by Rose E. Selfe. Edited by the Rev. P. H. Wicksteed. Crown 8vo, 6s.1906

[24] Šmitek Zmago: Kristalna gora : mitološko izročilo Slovencev / Ljubljana : Forma 7, 1998

[25] MISTERIJI. - [Slovenska izd.]. - Let. 19, št. 218 (september 2011), Ljubljana : ARA, 1993

[26] Pliny, the Elder; Bostock, John, 1773-1846; Riley, Henry T. (Henry Thomas), 1816-1878 Volume: 4, Subject: Natural history -- Pre-Linnean works Publisher: London, H. G. Bohn Year: 1856

[27] Slovene Legends and Signs / [selected and edited by Andrej Šiško; preface written by Andrej Šiško; illustrated by Beata Čop]. - Ljubljana: Amalietti & Amalietti, 2011 ([Ljubljana]: Atelje Pance)

[28] Slovenske pripovedke o kralju Matjažu / Ivan Grafenauer. - Ljubljana : Slovenska akademija znanosti in umetnosti, 1951 (in Ljubljana: Triglavska tiskarna).

[29] Malovrh, Miroslav: Kralj Matjaž: historical narrative/written by Fr. Remec. - Ljubljana: Narodna tiskarna, 1904.

[30] Virgil (comm. by W. V. Clausen) (1994). Virgil: Eclogues. Clarendon, Oxford University Press.

[31] Matičetov, Milko: Ivan Grafenauer, Slovenske pripovedke o Kralju Matjažu : SAZU, Razred za filološke in literarne vede. Dela - 4 (Inštitut za slovensko narodopisje - 1. Ljubljana

1951, 252 strani / Milko Matičetov. - Ocena knjige; V: Slovenski etnograf. - Letn. 6/7 (1953/1954), str. 311-320.

[32] The History of Herodotus Vol. 1, BOOK IV. The Fourth Book Of The Histories, Called Melpomene, Translated into English by G. C. Macaulay, 2000 Blackmask Online.

[33] Argonautica ; Cum Imp. Reg. et Belg¨y privilegio decennali / Ex conatibus Geographicis Abrah. Ortelii. - 1598 [erschienen 1624] Teil 36 des Gesamtwerkes in Abrahami Ortelii Theatri Orbis Terrarum Parergon; Sive Veteris Geographiae Tabulae : Commentariis Geographicis et Historicis illustratae / Tabulis aliquot aucta, et varie emendata atque innovata, Cura Et Studio Balthasaris Moreti, 1624

[34] William, Ryan & Pitman, Walter: Noah's Flood: The New Scientific Discoveries About The Event That Changed History. Simon & Schuster, 1997

[35] Koester, Helmut; Lambdin (translator), Thomas O. (1996). "The Gospel of Thomas". In Robinson, James MacConkey. *The Nag Hammadi Library in English* (Revised ed.). Leiden, New York, Cologne: E. J. Brill.

[36] Kalan, Valentin: O duši / Aristotel ; prevedel, napisal uvod in komentar ter dodal opombe in glosarij grških terminov Valentin Kalan. - Ljubljana : Slovenska matica, 1993

[37] Krause J in Terrien: KÉPES Biblia : szemelvények szentírási szövegek fiataloknak / [E. Krause J. és Terrien S. rendezték ; Káldi György S. J. fordította]. - Zagreb : Krščanska sadašnjost ; Zrenjanin : Bánáti Apostoli Kormányzóság, 1974

[38] Štiblar Martinčič, Draga: Anatomija in histologija : navodila za vaje /... [et al.] ; [urednica Draga Štiblar Martinčič]. - 1. izd. - Ljubljana : Medicinska fakulteta, 2007

[39] Joannes von Werd de Augusta, Rokopisni antifonar v 2 zvezkih, ki se nahaja kot stara posest v župnem arhivu v Kranju, August 17, 1491

[40] Čas M. 1981. Mogočna viharniška drevesa
in ostanki prakrajine med Raduho in Peco. Viharnik: 6-7

[41] Orožen Fr. [1901]: Vojvodina Kranjska. Prirodoznanski, politični in kulturni opis. [33 podob] / Ljubljana, Izdala "Matica Slovenska", Blasnikova tiskarna

Sources of images:

[pic.001] *Map from the ancient book 'Starodavni in današnji Slovenci'*
http://www.hervardi.com/images/venelin004bold.jpg

[pic.002] *A Venetian inscription from Würmlach*
http://www.reocities.com/ausslokon/image033.gif

[pic.003] *The giant Nimrod building the Tower of Babel*
http://www.tali-virtualmidrash.org.il/userfiles/tb03-salerno-tower.jpg

[pic.004] *Tower of Babel*
https://sites.google.com/site/crossbr/babel.jpg

[pic.005] *The beehive panel*
http://www.etno-muzej.si/files/oc/panjske_koncnice/em7289.jpg

[pic.006] *The place of God's departure back to heaven [A=Würmlach] – a large triangular formation, Satellite image*
http://maps.google.si/maps?hl=sl&tab=ll

[pic.007] *A large triangular formation, Satellite image*
http://maps.google.si/maps?hl=sl&tab=ll

[pic.008] *All seeing eye*
http://th03.deviantart.net/fs70/PRE/i/2012/087/b/f/all_seeing_eye_by_ifinch-d4u758z.jpg

[pic.009] *Measurements of satellite images*

[pic.010] *The City and the Tower of Babel - The European Parliament*
https://maps.google.si/maps?hl=sl

[pic.011] *The City and the Tower of Babel - The European Parliament*
http://ais.badische-zeitung.de/piece/00/3c/44/74/3949684.jpg

[pic.012] *Little 'Sphinx' or 'big pussy-cat'*
http://s8.mojalbum.com/493038_9481165_9481364/montaz-spik-nad-policami/jejmene-ustvaril-sem-malika.jpg

[pic.013] *A big 'Window'*
http://www.gore-ljudje.net/objave/gorazdgor/shpns_10.jpg

[pic.014] *'Double Window'*
http://www.gore-ljudje.net/objave/gorazdgor/shpns_36.jpg

[pic.015] *'Lego bricks'*
http://primozblaha.files.wordpress.com/2011/10/63-legokocke.jpg?w=1200&h=

[pic.016] *Megalits on top of a mountain Špik*
http://www.gore-ljudje.net/objave/gorazdgor/shpns_33.jpg

[pic.017] *Megalits on top of a mountain Špik*
http://www.gore-ljudje.net/objave/gorazdgor/shpns_48.jpg

[pic.018] *Megalits on top of a mountain Špik*
http://www.gore-ljudje.net/objave/pikon/IMB_7065.jpg

[pic.019] *Demolished megalithic temple Metulum*
Page 19 on http://www.misteriji.si/art/Letnik_2011/Misteriji_218

[pic.020] *Demolished megalithic temple Metulum*
Page 21 on http://www.misteriji.si/art/Letnik_2011/Misteriji_218

[pic.021] *Stone mushroom*
http://www.destinacije.com/Slike/Slovenija/PlanineiVrhovi/Kamnita_Goba.JPG

[pic.022] *Tomaž's Table*
http://zanimiv.net/blog/gumpi/files/2009/08/p1050989.jpg

[pic.023] *King Matthias and his knights on the beehive panel*
http://www.etno-muzej.si/files/oc/panjske_koncnice/em2339.jpg

[pic.024] *King Matthias, the ruler of the Golden Age indeed showed up on Mount Peca in 2006*
http://images.24ur.com/media/images/600xX/Aug2006/16129038.jpg?d41d

[pic.025] *King Matthias, the ruler of the Golden Age indeed showed up on Mount Peca in 2006*
http://images.24ur.com/media/images/600xX/Aug2006/16129039.jpg?d41d

[pic.026] *Goddess Ishtar and all-seeing eye*
http://www.bhagavadgitausa.com.cnchost.com/INNANA-ISHTAR.gif

[pic.027] *Holy Lady on the ancient cathedral of Carantania, the first Slovenian state – 'Gosposvetsko polje'*
http://2.bp.blogspot.com/-6aqg20OSow4/TnblZtvCekI/AAAAAAAAJuY/25-u9gVC-t4/s1600/gosposvetsko031.jpg

[pic.028] *Reconstruction of the Garden of Eden according to the record in the Bible*
The copyright work of Irena Pangeršič

[pic.029] *Ister, also known as Savus, on Abraham Ortelius' map from 1624. Easter/Ister is the second name for Ishtar or Astarte, "the Queen of Heaven or Eden Queen."*
http://upload.wikimedia.org/wikipedia/commons/d/de/MapoftheVoyageoftheArgonauts.jpg

[pic.030] *The deep bed of the former river under the Black Sea from the Mediterranean through the Bosphorus*
http://www.ziaristionline.ro/wp-content/uploads/2010/08/Black-Sea-Marea-Neagra-undersea-river-Univ-of-Leads-Roncea-Blog.jpg

[pic.031] *Part of the structure of large settlements under the Black Sea*
http://www.youtube.com/watch?v=TP75z6NjBMY

[pic.032] *Reconstruction of the Garden of Eden according to King Nimrod's regional planing of Tower of Babel in shape of the* all-seeing eye *of God*
The copyright work of Irena Pangeršič

[pic.033] *The two-headed blue and golden Phoenix on the coat of arms of the Province of Carniola and the one-headed red and golden Phoenix on the coat of arms of Kranj in the code: "The Kranj Antiphonary" writer and illuminator Ioannes von Werd de Augusta, August 17, 1491.*

Microcosmos in Macrocosmos and How Great is Allah?

Microcosmos in Macrocosmos and How Great is Allah?

Irena Pangeršič
MA and BS in architecture, DipHE in Civil Engineering
e-mail: ariel.aneri@gmail.com

»Fractal geometry will make you see everything differently. There is danger in reading further. You risk the loss of your childhood vision of clouds, forests, flowers, galaxies, leaves, feathers, rocks, mountains, torrents of water, carpets, bricks, and much else besides. Never again will your interpretation of these things be quite the same.« Barnsley, Michael F.,*Fractals Everywhere*Chapter I (p. 1) Academic Press, Inc. San Diego, California, USA. 1993; inGaither [1]

Abstract: For us, nature is a multitude of phenomena that sometimes appear coincidental and chaotic, and to understand the entire reality, we use several scientific theories, philosophies and religious views that we observe and compare to our own mental models which mostly do not let us perceive the whole only as one reality and we are, when it comes to physical nature and dynamics, under the influence of scientific models that treat reality as a kind of machine, consisting of an unimaginable number of parts that influence each other under certain static and physical laws. The creation of a single, final theory that would explain the existence of all matter, energy and natural forces is getting closer today with the standardisation of quantum theory and general theory, or "the theory of everything". However, despite the scientific progress and optimistic search of a scientific "theory of everything", we increasingly feel that something is missing and it will stay missing until we try to form our view of life only on the basis of science. "We are, in fact, forced to accept scientific absolutes with unconditional trust – in a similar way that we accept religious beliefs. It is not possible to prove that speed of light is constant and unsurpassable any better that it is to prove the existence of God." [2]. Thus, if we are finding out that sciences cannot offer all absolute truths that would guide us, and that religions are not all about superstition, we could find out that sciences and religions could complement each other. Religions consist of secrets that are inaccessible to science all the time, while sciences contain understanding that would remain secret any way. Furthermore, answers need to be sought also in the connection between physical structures of nature and creations of the human hand, in the conjunction of elements of social activities and processes.

Key words: biological fractals, operation of swarms, dimensions of space and time

The nature of the world, perceived with senses [sight, touch, taste, smell and hearing] is, in fact, unidentifiable and the "fundamental question is how, when and into what it changes, and why it sometimes does not. [...] The form therefore acts as a principle that organises [coordinates] disharmonies of opposites and disorder [...] the urban area, the spatial unit and at the same time the entire world – and here, space and time as fundamental concepts that influence our ways of understanding the existence of the world ..." Similarly to the geographer Dr. Andrej Černe, also the sociologist, Dr. Drago Kos determines: "it is practically impossible to cover all symbolic and semantic, essentially worldly dimensions of space. Three basic coordinates might

suffice in geometry or geodesy, while the social space is much more curved and it is therefore more difficult to analyse. At the same time, space is also sensually and explicitly concrete, as well as abstract and conceptual. It can be generally available or totally exclusively closed, so to speak locked, it can be totally individualised or generically unspecific etc. In modern empirical and also theoretical tradition, this is a problem that exceeds the known methodological instruments" [3]. The still hidden nature is also presented in: The Gospel of Thomas, in own words of Jesus Christ: » '1' … Whoever hears these words shall never taste death … '3' … the Kingdom of God is inside of you, and it is outside of you … '77' … Split a piece of wood, and I am there. Lift up the stone, and you will find Me there … « [4]. A riddle on the true image of the nature of the world and its solution is actually equally exciting as the story about Rarg:'A land so perfect that the sun never rose until it was absolutely sure that everyone was awake. Everybody was happy in Rarg until one day an astonishing discovery was made that was to change their lives. The Rargians discovered that they are just a dream'… [5].

Biologistic society: The inseparable addressing of social, natural, cultural and economic environment can be found in the so called biologistic theories for which it is characteristic to contain factors and mechanisms which occur in biology and have a holistic view of reality. The thesis about society and the reflection of social activity in the common social, natural, cultural and economic environment as a living organism including basic and more complex forms, or as a super-organism, which develops in an organicistic and evolutionistic way, is presented by Spencer [6] as the founder of socio-biology, and Geddes [7] as a biologist and theorist and the father of modern city planning. Organicistic theories about the nature of society were already present in Plato's Republic with the statement that the same laws apply to the individual and to society ... as written by MacDonald [8]. Identical theories are also written in the Manu holy books, namely that castes originated from different parts of the Creator's body [9]. Organicists Lilienfeld [10] and Schäffler even tried to prove that society is in fact an organism, where they tried to find out how the nervous system corresponds with the government, the transport with the vascular system and which organ in the human society would correspond with individual organs in a live organism. J. K. Bluntschli [11] also agrees with their theory, claiming that the state lives as an organic formation or as a combination of legislation and politics, which operate reciprocally. Scientific research studies of organic state formations can also be studied according to the philosophy method and the method of historic facts, considering that the state as a moral organism is not a product of cold logic, as the legislation is not a collection of speculative opinions. [11]

The State – homeostatic organism.According to H. Spencer's theory, the state – as an organism – is homeostatic [12], which means that the change in one part triggers a change in other parts in order to keep the system in balance. It develops in a similar way as other organisms in evolution, i.e. from simple forms to more complex ones. The human society, however, is – as an organism – the most perfect evolutionary formation [13]. The concept of creation which operates as an organism is also adopted by Leonardo da Vinci, who is convinced that by knowing the function of the human organism we can apprehend and understand the operation of the entire universe. [14]. Even the condition to create an ideal society was already seen by Renaissance architects in the design of the ideal city, built according to the patterns and measurements of the human proportions, in order to ensure order and harmony [15] to the society through the ideal city structure. The Renaissance thought of the human organism as an ideal city is continued and researched by Patrick Geddes [7]. According to Geddes, the planning has to start with an analysis of real conditions in the region, with resources in the region and the human response to these resources, as well as an analysis of their complex consequences, shown in the cultural landscape. The analysis of real conditions before the actual plan was Geddes's motto. The region represented a basis for the renovation of the social and political life. With this, Geddes provided a substantive framework for the thinking of numerous other regional and other planners [16]. Following Geddes, further research of city structures is adopted and continued by Lewis Mumford whose thinking also

influences Frank Lloyd Wright, who is – according to many – the founder of organic architecture and one of the most passionate defenders of regional planning.

Organic planning.As a new challenge and response, organic planning is supposed to set on its rails the current chaotic scenario, where urban planners are losing their last battles of a legitimate relationship towards spatial planning. Space should be planned and constructed on the basis of individual needs, individual findings and within a modern development which is not hostile to our natural and cultural heritage. Mumford also presents an argument about how and why these organic-society and space based formations are made: "Due to an increase of brain growth, which directly exceeded the human's direct functional needs, the human was capable of developing new organs outside his body, without being attached – as in other organic adjustments – to an infinite continuation of these organs. By remaining non-specified, man opened a thousand new ways for himself and for a further development." [17] "While other organisms only need as much past as they carry in their genetic codes, and only as much environment as is available, the real human capacity depends on their access to more distant events, those coming from memories or those projected into the future, as well as to more distant or inaccessible parts of the environment. When materialisation is created, it is not possible to achieve with direct efforts any equal quantity of experience within the limits of only one life." [17] "Organic planning does not start with a pre-designed intent; it develops and moves based on individual needs, individual opportunities, in a long line of adjustments that become more and more consistent and efficient, so that in the end they create a complicated final design of a sketch, which is hardly less uniform than the pre-designed geometric pattern." ... "Those who refuse organic plans as unworthy of their name, confuse pure formalism and correctness with efficiency, and incorrectness with spiritual confusion or technical incompetence." [17]

Man – the original plan of creation. Also the holistic-sophistic, philosophically oriented anthropocentric view places man in the centre of action. It gives him the role of honour, i.e. seeing man as a plan of everything that exists. Holy geometry or the original plan of creation can be found both in the golden cut as well as in the system of Mandelbrot's [18] fractal and in holographic theory, according to which every part of the holograph contains all necessary information for the description of the overall state. Even Kabbalah comes close to Protagoras's statement that man is the measure/measurement of all things and all processes, when it offers in its tree of life a holistic explanation of man as a microcosm in a macrocosm. Pantheism is not far behind, equating the Creator with the creation – here also the anthropocentric principle needs to be taken into account = man is not only the culmination of creation, but also its master. Still, despite man's presence elsewhere than on Earth, anthropocentrists do not perceive themselves to be masters of the solar system or masters of the universe or the multiverse. The anthropocentric view on man as the master of creation, also adopted by Judaism, Christianity and Islam, can also be compared to the non-compliance of relativism in the sense of awareness that for our existence other forms of life are also important, and that social an mutual relations and the care for nature are not separate elements, considering they are co-dependent and as such reach the whole world within the concept of globalisation.

Hypotheses.HYPOTHESIS 1: The creativity of the geo- and bio environment of Nature operates as a workshop where social individuals are the co-creators who – with their social, cultural, and economic interventions in space – structuralistically co-create the developing dynamic supra-organism. HYPOTESIS 2: The geo- and bio- natural structures on Earth with their cycles and development phases, complemented by collective and individualistic adjustments and co-creation of habitat coevolutionary structures, gradually change into more perfect and more sophisticated forms and readable multi-dimensional, and more and more time-concentrated and fragmented projections that allude to the organic evolutionary form of the dominant individual. HYPOTHESIS 3: The antagonistic and reductionistic approach and intervention into space which does not consider the holistic and synergic structurally interdisciplinary and potentially perspective procedures of planning, causes an effect of static and instable inner states that is reflected – in a combination of natural and social habitats – as

a statistically critical deviation, where the union of all deviations can also be reflected as a total escalation and collapse of the systems that preserve us, enrich us and develop the past, present and futuristically oriented social and cultural development.
HYPOTHESIS 4: Different developmental, multi-dimensional interdisciplinarily shaped forms indicate in a semiotic way and with a conductor orientation the needs and efficiency of planning, which can only result prosperous with adjustments to an individual form, while at the same time the positivity of the first tradition is restored and, if needed, the energy of polarisation annihilation can be enriched and used. HYPOTHESIS 5: The synergy in the guidelines of spatial planning with the use of sophisticated structures of organic planning is the interdisciplinary connection of multilayer levels into a holistic whole, which protects multiculturalism and the habitat bio- and geo- diversity, while specialisations of individual sciences are still implemented in their strict reductionism, which leads to an even more perfect understanding of the whole. PREVIOUS HYPOTHESES: The Earth is a living creature, a hypothesis supported already by numerous thinkers through all historic periods: Pythagoras, Democritus, Plato, Aristotle, Leonardo da Vinci, Descartes, the pioneer of modern time, Dr. James Ephraim Lovelock, and others.

The Earth fractal and the Homo sapiens sapiens fractal. Even the characteristic feature of the Homo sapiens sapiens fractal is shown in the infinite geometric complex structure, where a certain level of self-similarity is already detected, but not always equally expressed. In certain basics it is expressed as a real or physical fractal, in others as an exact or mathematic fractal. The difference between them is that self-similarity in mathematic fractals only exists on a truly small scale, which means that their fractal structure is expressed also when $\varepsilon \rightarrow 0$, while in real fractals this self-similarity finally ends with a big ε. There are a great number of real fractals in nature and some of the typical examples are listed here: mountain ranges, outlines of coasts, clouds, large rivers deltas, cities, network of blood vessels, the heartbeat, ferns, blades of grass, treetops, cauliflower, broccoli, etc. Of course, you will not be able to see self-similarity in these systems without imagination. It is much easier to notice this characteristic in mathematical systems that have fractal solutions for certain parameter values. These systems occur in social and political structures, whose peak is represented by the state homeostatic system where certain formations are already connecting into more highly developed formations that are more easily traceable as visually pure mathematical fractals. However, because the Earth fractal is – as the Homo sapiens sapiens fractal – a time-space fractal, it is also necessary to consider the deviation from the real formation due to the phase age factor [because not all homeostatic formations are completely shaped, this indicates a very early, actually fetal stage of development of the Homo sapiens sapiens.]

Behavioural models.A record of apparently complex behaviours of natural phenomena with the use of procedural models [computer programmes] which include actions and autonomous characteristics of virtual worlds – based on repetitive behaviours of birds – was presented by Craig Reynolds with his implementation of the *Boids* programme [based on 19, 20]. He presented movements on the basis of three basic rules: separation, alignment and cohesion. This kind of approach meant a great step forward in comparison to traditional techniques used in the film industry or, more precisely, in all types of computer animations in the 80s of the previous century. Prof. Dr. Forest Kenton "Ken" Musgrave (aka Doc Mojo) entered history with the construction of fractal planets, recreating with a fractal construction of virtual reality: multifractal terrain models, static erosion gradient fields, ontogenetic geometric atmospheric density, proceduralism [it abstracts copious detail into a compact set of instructions for its reproduction] and with the capability to explore these worlds interactively.A progress in the expansion of the basic Reynolds model is presented by Delgrado-Mata [21] who expanded the basic model and included the consideration of the effects of fear, and by Hartman and Benes's [22], whose model presents complementary forces in algorithm alignment, which they called "change of leadership" – a force that enables each agent to become the leading one and try to escape, etc. [based on 23]. Here we could look for a fractal connection of bio-life with artificial intelligence, through the basis of which an interconnection between psychology,

neurology, mathematics, logics and other sciences – with the purpose of making a machine that would imitate humans' thinking, emotions and consciousness – was already conceived in the 40s of the previous century by John von Neumann [24] in his researches of advanced computer architectures with a foundation on parallel processing. He named this structures "cellular automata" [CA] – whose basic characteristic was its inner state that can be changed through discrete time steps by the cell, based on its own state in the previous step, and on states of its neighbouring cells in the previous step.

This type of behavioural models, called the CA can be compared – fractally speaking, seen through a time component – to the development of the red blood cell – the erythrocyte [i.e. a smaller version of the real physical fractal, the Homo sapiens sapiens], whose developmental phases are also based on the changing inner state, while these phases of the changing cell [aka cellular automata] act exactly in the opposite direction – from the most complex to the simplest inner state, also becoming smaller in each transformation [this is the degradation of size from 60 μm to 6 μm]. And if we draw a parallel here with the development of the human race: could we therefore say that this is a degraded race of giant ancestors, whose achievements and capabilities were once something to be envied? This hypothesis can also be silently proved by giant architectural creations from around the world [25]:

- 200 ton blocks at Ollantaytambo and Ollantayparubo, Peru
- 100 to 200 ton foundation and wall blocks of Puma Punku, Tiahuanaco, Bolivia
- 340 ton 65 feet high standing stones of Brittany, France
- 2000 ton foundation stone, and 1000 ton 180 foot stones fitted 20 feet up in the building at the Temple of Jupiter, Baalbek, Lebanon
- 50 to 300 ton blocks of Sacsayhuamen, Peru, fitted precisely
- Walls 40 feet thick, Chan Chan, Peru
- Stone heads the size of a 7-storey building, on Easter Island
- 25 to 50 ton blocks at Stonehenge, England
- geometrically shaped blocks at El Enladrillado, Chile:12 to 16 feet high, 20 to 30 feet long, and weighing several hundred tons
- 170 ton stone tomb on Tonga Tabu, Pacific Ocean
- 65 foot giant statues, at Thebes, Egypt
- Statue 18 stories high, Bemian, Afghanistan
- 20 ton blocks of Bosnia piramids

And instead of looking for sophisticated and complicated ways how these architectural structures were built, it would be better to ask: Why would 'little people' of an average height of 6 feet make superhuman effort to build structures that could only be used by giants? As prophet Hadith says in 4:543 and 4:544 of the Narrated Abu Huraira [26], the first man, i.e. Adam, was 60 cubits tall – this is ten times more than the average height of the Homo sapiens sapiens today.

Fractally speaking:

- The range of erythropoiesis of the erythrocyte is from 60 μm to 6 μm
- The maturation of the Homo sapiens sapiens according to Hadith's records is from 60 cubits to 6 feet[taking into account that a part in this unique developmental state can also be attributed to the creation of our only satellite – the Moon – and its distance from Earth, which was not always the same as it is today ...]:

The fact that people of the past were of immanent size, and were eventually degraded both in their figure as in their strength, is present in myths and archaeological findings around the world. The giants were always the topic of discussion in ancient records:: Numbers 13,32-33 [27];Judith 16,7 [28]; Wisdom of Solomon 14,6 [28]; Sirach 16,7 [28]; 3 Maccabees 2,4 [29]; 2 Samuel 21,20 [28]; Chilam Balam Of Chumayel [30]; 1 Baruch 3, 26 [28]; Plutarch's parallel lives: Theseus 36 [31]; I.Herodotus 68 [32]; II.Herodotus 155 [33]; III.Herodotus 82 [34]; Flavius Josephus Book I, Ch 3, 1 [35]; Flavius Josephus Book I, Ch 9 [35]; Flavius Josephus Book III, Ch 14, 2 [35]; Flavius Josephus Book V, Ch 2, 3 [35]; Flavius Josephus Book VII, Ch 4, 1 [35]; Flavius Josephus Book VII, Ch 12, 1-2 [35]; ...

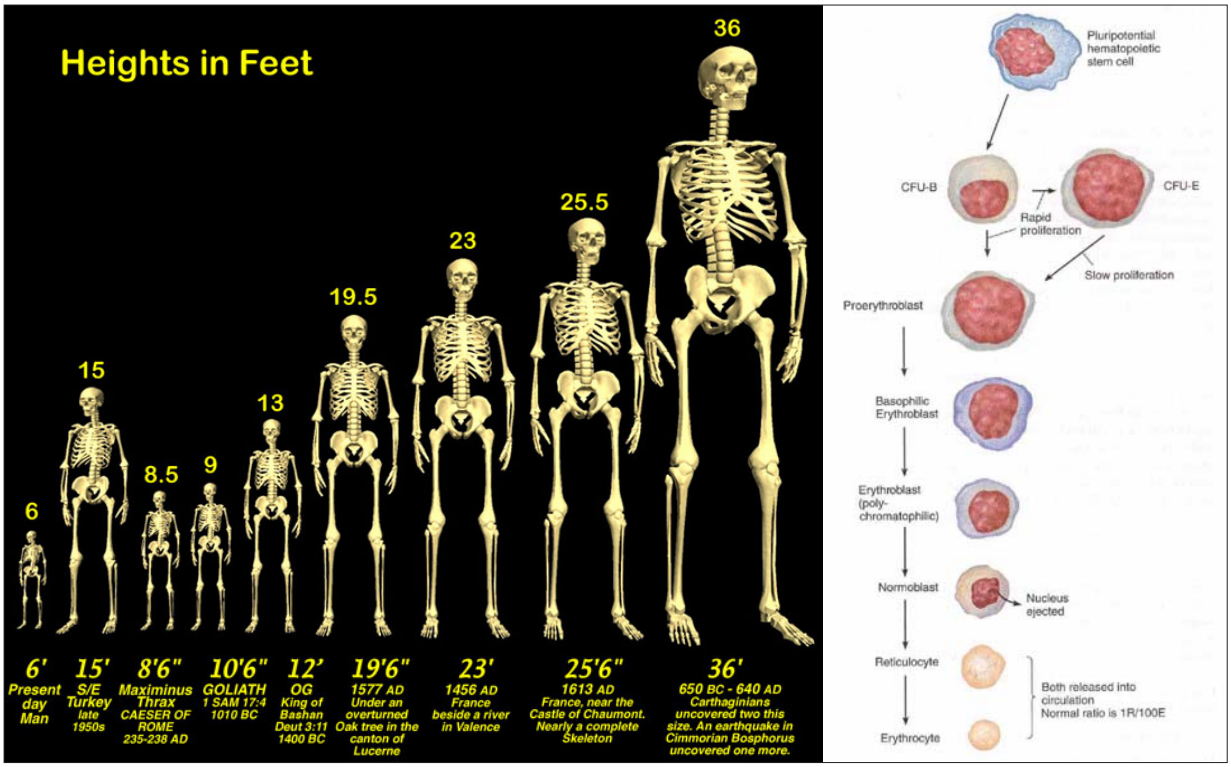


Table 1: Very first people of immense stature later degenerated in size and vigour + Erytropoesis

Some cultures count with more than five previous worlds. For example, we learn from a Hebrew tradition called 'Shmi Tot' [36] that each of the previous worlds was destroyed in a cataclysm. The Jews believe that the world exists in cycles and each ending of a cycle is considered as a transformation. A Jewish legend tells:
»Nor is this world inhabited by man the first of things earthly created by God. He made several worlds before ours, but He destroyed them all, because He was pleased with none until He created ours. But even this last world would have had no permanence, if God had executed His original plan of ruling it according to the principle of strict justice. It was only when He saw that justice by itself would undermine the world that He associated mercy with justice, and made them to rule jointly.«

'Shmi Tot' [36] states that Noah's great-great grandfather Enoch, who lived before the great Flood, actually lived in the seventh creation of this world and that today's eighth creation can become perfect even without a cataclysmic demolition if the entire community proves to be worthy of this in front of the Creator. With a fractal parallel we can once again relate to the developmental groups of the erythrocyte: even the 8th developmental stage [i.e. the reticulocyte], similarly to the red blood cell – the erythrocyte – does not have a nucleus, but is still not perfect and approximately 1% of these can already circulate in peripheral blood. The fractal erythrocyte goes through 8 stages of development in its maturation from 60 µm to 6 µm, to reach perfection only at the 9th stage. [1. The pluripotent stem cell, 2. The multipotent stem cell of myeloid lineage, 3. The directed stem cells of erythroblast lineage, 4. Pronormoblast, 5. Basophilic normoblast, 5. Polychromatic normoblast, 6. Orthochromatic normoblast, 8. Reticulocyte and 9. Erythrocyte] [Table 1],... and how this perfection can be seen in our world ... is presented by the Coptic Gospel of Thomas '18', in Jesus's own words: [4]: ... »When you make the two one, and when you make the inside like the outside and the outside like the inside, and the above like the below, and when you make the male and the female one and the same, so that the male not be male nor the female female; and when you fashion eyes in the place of an eye, and a hand in place of a hand, and a foot in place of a foot, and a likeness in place of a likeness; then will you enter [the Kingdom]« ...

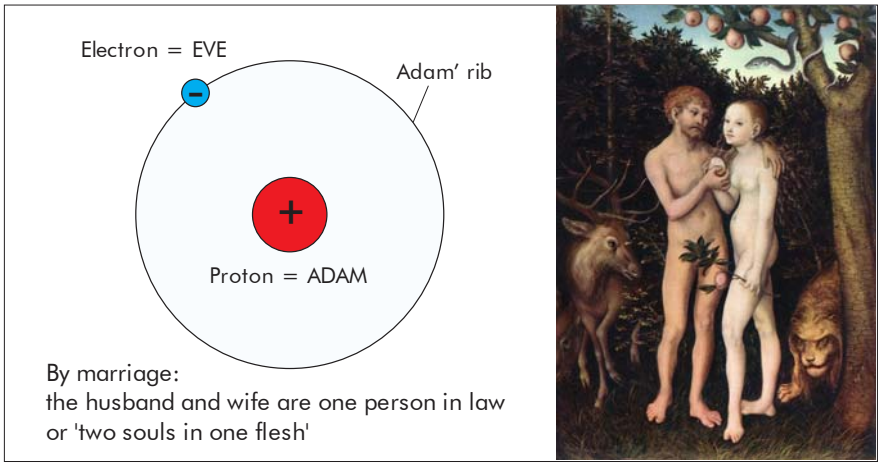


Table 2: First Matryoshka fractal: Hydrogen atom - Eve was created from Adam's rib [the rib is in Hebrew called "CELA" (cell structure); http://www.studylight.org/lex/heb/view.cgi?number=06763]

In order to understand the meaning of these words, we have to know the fractal rate that is smaller than the erythrocyte ... the hydrogen atom ... ἄτομος : átomos – meaning indivisible. The hydrogen element which is composed of one proton [+] and one electron [-] is basically only one indivisible unit [Table 2]which is represented on a higher fractal level by the erythrocyte, in which the cytoplasm [-] and the nucleus [+]can no longer be defined.

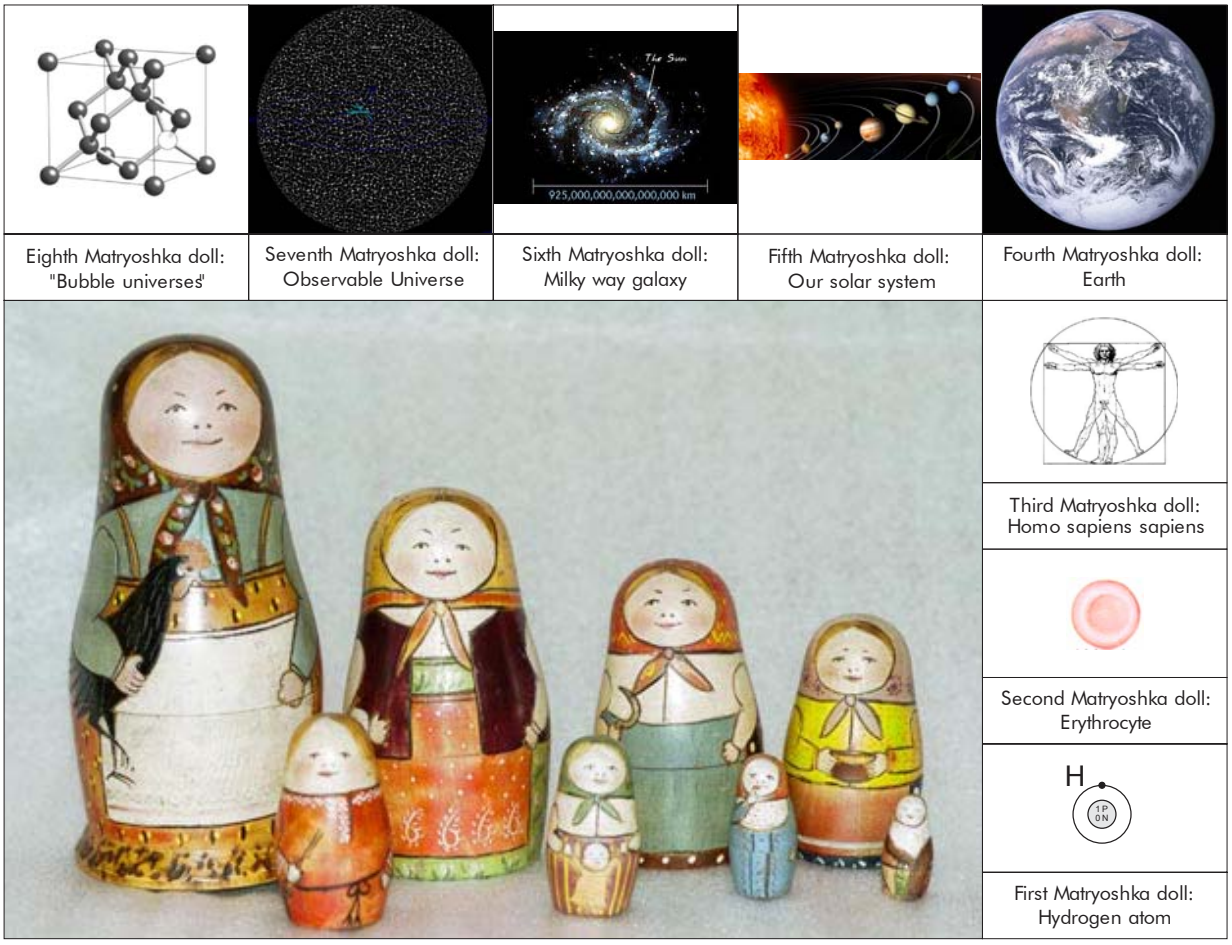


Table 3: The "matryoshka principle" is also an example of Mise-en-abyme - the onion metaphor for a self-similar.

This is how we get the basic story which lead to the "big bang": ... nuclear fission ...when each of us lost the love of their lives ... And ... nuclear fusion ... when we once again regain the trust of the Creator, he will enable us to find the love of our life again ... and before we return home, where are origins are, our last test shall be: "two who live as one", i.e. the so called celestial marriage which is also discussed in The Revelation.

Plato mentioned this particular state 2,500 years ago: ... »And when one of them meets with his other half, the actual half of himself ... if this is what you desire, I am ready to melt and fuse you together, so that being two you shall become one, and while you live live a common life as if you were a single man ... this meeting and melting into one another, this becoming one instead of two, was the very expression of his ancient need ... and the reason is that human nature was originally one and we were a whole, and the desire and pursuit of the whole is called love. There was a time, I say, when we were one, but now because of the wickedness of mankind God has dispersed us ... for if we are friends of God and at peace with him we shall find our own true loves, which rarely happens in this world at present ... each one returning to his primeval nature had his original true love, then our race would be happy ... we must praise the god Love, who is our greatest benefactor, both leading us in this life back to our own nature, and giving us high hopes for the future, for he promises that if we are pious, he will restore us to our original state, and heal us and make us happy and blessed« ... [37]

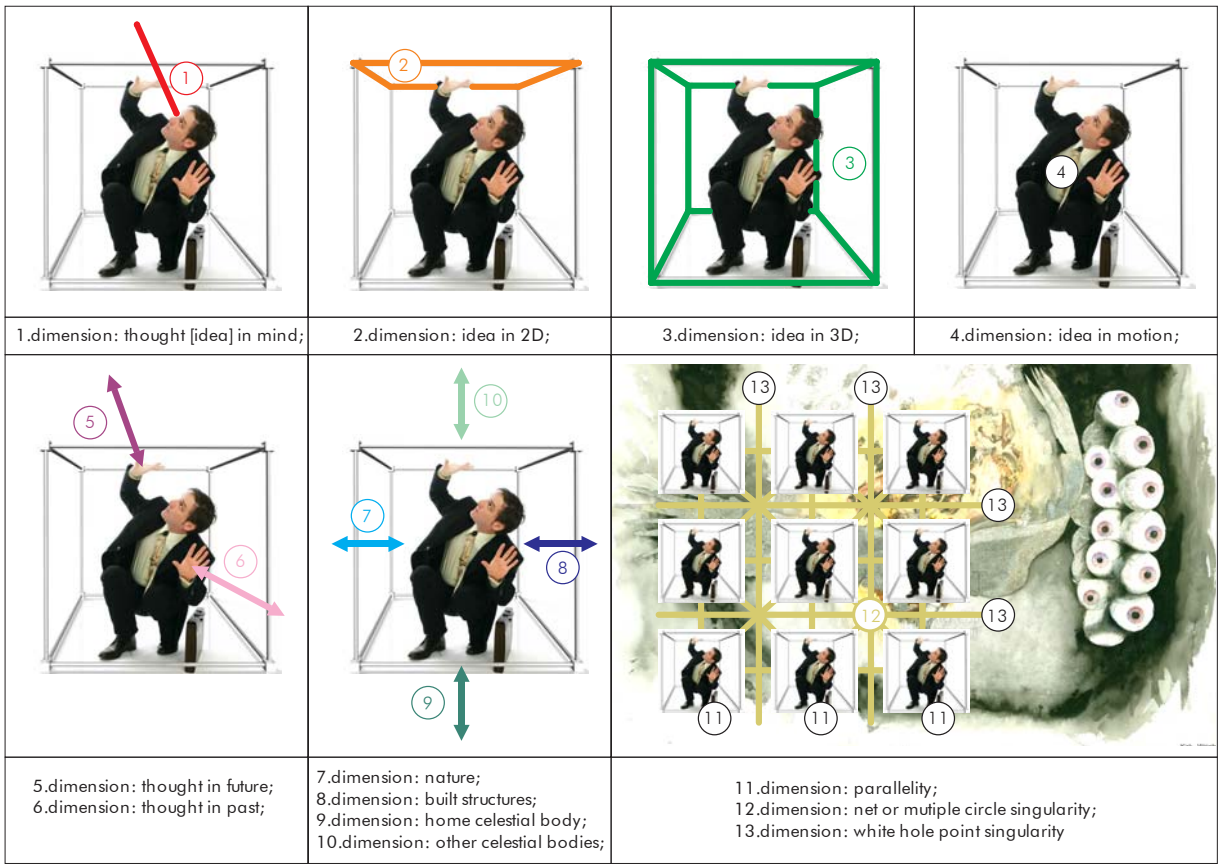


Table 4: Thirteen dimensional controlled growth of time-space bio fractals - in each higher dimension we see more

<u>Dimensions and time-space structural connection.</u>The explanation that enables such establishment of a time-space Homo sapiens sapiens fractal can, in fact, be sought in the always unfinished "symphony" of understanding the one that holds everything together, i.e. the force that obviously controls growth, diversification and complexity of such a system.

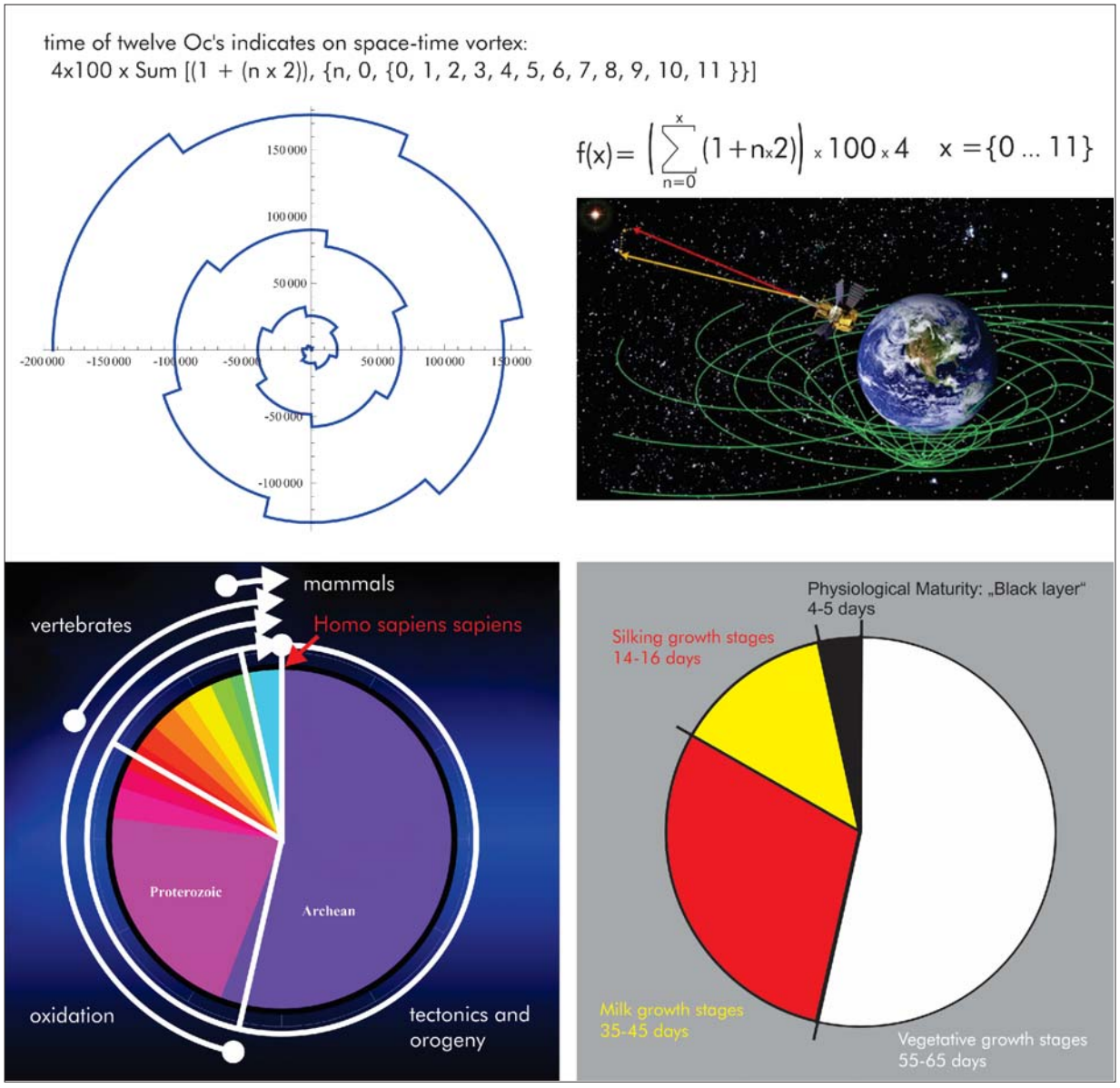


Table: 5: Time and space of twelve Oc's of Chilam Balam Of Chumayel And Popol Vuh presentation: Corn Growth Stage Development = Homo sapiens sapiens Growth Stage Development

The dimensions in this case will be called "the eyes[1]" [or thirteen»Oc« as Chilam Balam Of Chumayel calls them in his prophecy[2]] [30], since every additional dimension enables a new perspective, which enables us to "see more" than in the previous, lower one. Here, we shall not

[1] Eyes or individual dimensions – i.e. the 13 dimensions of time and space

[2]Thus it was recorded <by> the first sage, Melchise<dek>, the first prophet, Napuc Tun,the priest, the first priest. This is a song of how the *uinal* came to be created before the creation of the world. Then he began to march by his own effort alone. Then said his maternal grandmother, then said his maternal aunt, then said his paternal grandmother, then said his sister-in-law: "What shall we say when we see man on the road?" These were their words as they marched along, when there was no man <as yet>. Then they arrived there in the east and began to speak. "Who has passed here? Here are footprints. Measure it off with your foot." So spoke the mistress of the world. Then he measured the footstep of our Lord, God the Father. This was the reason it was called counting off the whole earth, *lahca* (12) Oc. This was the count, after it had been created by 13 Oc, after his feet were joined evenly, after they had departed there in the east. Then he spoke its name when the day had no name, after he had marched along with his maternal grandmother, his maternal aunt, his paternal grandmother and his sister-in-law. The uinal was created, the day, as it was called, was created, heaven and earth were created, the stairway of water, the earth, rocks and trees; the things of the sea and the things of the land were created.

forget about Witten's analysis which showed that the universe, according to the M-theory, has 11 dimensions which, unfortunately, no one has yet seen [38], especially because our understanding of theory is so incomplete that nobody knows whether the story ends here, or if the theory is actually correct and this shall be the last Russian babushka, or if all this is composed of even smaller parts [Table 3].

Today's scientists, in fact, do not have any definite ideas to explain what ultramicroscopic elements of time and space actually are [38]. Therefore, let us look at this through the eyes of the architect and/or civil engineer [Table 4].

The comparative fractal time component of Homo sapiens sapiens's creation is given to us by Popol Vuh, who revealed the secret that 'the human matures like corn'[3] [Table 5].

The state of development of the Earth – Gaia, as a greater and more complexly readable fractal of the Homo sapiens sapiens organism. On the basis of methodology that represents the Homo sapiens sapiens evolutionary constants as a plan of creation, in the geological development of Earth and in the world politic consolidation there are currently already readable structures and systems. In the last minute – after the appearance of the human's presence on Earth [seen through a geological division of planet Earth's development in 24 hours], these have shaped, with fights, conquests, subjugations and finally today also with a peaceful consensus, into a real and visually readable humanoid hermaphrodite organism that currently consists of: [1] the endocrine system of six glands: the hypophysis, the thyroid, the right adrenal gland, the salivary gland, the reproductive gland, gland hormones and some tissue hormones; [2] the digestive organs: the oral cavity, the esophagus, the stomach, the colon, the cecum, the small intestine, the anal canal, the liver, the gall bladder, the pancreas; [3] the respiratory organs: the throat, the trachea, the lungs, the diaphragm and the vocal cords; [4] the skeleton: the spine, the chest, the skeleton of the upper limb, the pelvis and the skeleton of the lower limb, the cranial bones; [5] the circulatory system: the heart [Table 6],

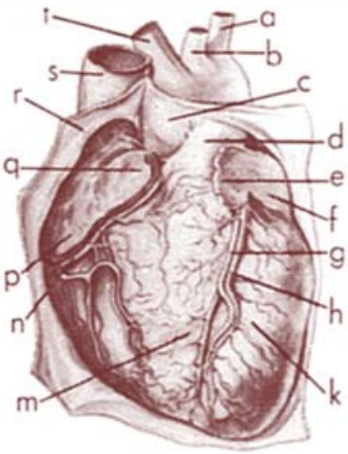
HUMAN HEART	EARTH HEART [Middle east]
	
[m] - right ventricle; [k] - left ventricle [p] - right atrium; [f] - left atrium; [s] - Aorta	[Saudi Arabia] - right ventricle; [Iran] - left ventricle [Egipt] - right atrium; [Turkey] - left atrium; [river Nil] - Aorta

Table 6: Fractality - Human and Earth heart

the aorta, the vena cava, the arteries and the veins; [6] the nervous system: the cerebrum, the cerebellum, the spinal cord; [7] the lymphatic system and spleen; [8] amino acids: 51 amino

[3]Corn matures approximatelyfor 120 days = the life span of erythrocytes is approximately= 120 days = the years of man [Biblija, Genesis 6,3] [28]; And He said 'My spirit shall not always abide on man; for they also are flesh and their days shall be one hundred and twenty years'. [The Book of Jubilees 5, 8-9] [28]

acids of insulin, 8 essential amino acids and 12 non-essential amino acids; [9] the urinary system: the kidneys, the bladder and the left adrenal gland; [10] the developed sex organs of both genders; the male reproductive organs: the testicle, the scrotum, the seminal duct, the penis and the prostate with semen; the female reproductive organs: the womb, the ovary with the oviduct, the vagina; [11] the skeletal muscle: head muscles, neck muscles, body muscles, lower limb muscles, upper limb muscles; smooth muscles, heart muscles, circular muscles;[12] the fetal development: the yellow body and the placenta – contemporary presence of the yellow body and the placenta, and the development up to the point described above ... indicates the age of the organism, i.e. the 12-week old fetus.

Methodology – Evolutionary constants of the Homo sapiens sapiens; they are cultural-evolutionary genetic replicators called "MEMs" which are passed on from generation to generation, and from one place to another with a written and oral word, by personal example and other types of influences [adapted from Popper, K. in Dawkins 39]. The latter practically represent 24 karyotypes in our genes. Space through time and the development of the organism through time defines 22 constants + the XX or XY gene in its development to determine the sex – i.e. a total 24 constants.

To explain the concept of urban, in fact, we must first define the space with characteristics that define it in its geographical infinity with all geomorphic changes, as well as with space that has limits and defines the settlement area. It is the changeability of both of them together that defines the unrepeatable cultural landscape in the final stage. When searching for the meaning of the settlement area, Dr. Alenka Fikfak [40] presents 20 evolutionary constants that ensure the system of stability: 1. SPATIAL: terrain, water, light, climate, vegetation, population, construction; 2. TECHNOLOGICAL: technology; 3. ECONOMIC: infrastructure, links, market, activities; 4. SOCIAL: demography, culture; 5. SOCIO-POLITICAL: socio-political framework, normative and administrative criteria; 6. ECOLOGICAL: environment protection; 7. CULTURAL AND ESTHETIC: the influence of the environment, the style of buildings, shapes of houses and cultures.To enable a methodological determination of urban space measures, the 20 already defined constants should be completed with 8. EVOLUTIONARY-CONCEPTUAL CONSTANT, i.e.:The conceptualisation of space organisation – anthropomorphic personification of the 'animus'; Sampling of spatial organisation – anthropomorphic personification of the 'anima', and as the last genetic evolutionary replicator constant that determines our "pole" or orientation, there is the9. NUCLEATION – DISPERSION CONSTANT which defines the gender of the location's spirit, "genius loci", i.e.:Nucleation – the 'genius loci' determines the XY chromosome constant of the space; Dispersion – the 'genius loci' determines the XX chromosome constant of the space.

Conslusion.Ethics and morality meant the same thing in the past: a residence, a habit, a custom and character. Today we could call it a responsible use of the environment, space, sources and values. However, the empirical analysis of economic, social and environmental development characteristics of European countries reveals that the existing development trends are non-sustainable and are moving away from the set strategic goals. Due to favouritism of quantity indicators of generalised scientific research criteria, the holistic approach – encompassing the understanding of relations of everything towards everything through elements of art, aesthetics, quality, technical perfection, culture and ecological awareness – is being neglected. The influence of the crisis in one sector is spreading into other sectors, and the crisis of one country is spreading into other countries.In theory and in praxis we come across the fact that the world is a homogeneous whole, whose connection should be built on diversity and cultural and historical achievements of all nations across the world.

The current development stage of the Earth fractal indicates the age of the organism, i.e. the 12-week-old fetus; this is the time when the bone marrow of the fetus starts to produce its own red blood cells; and also the time when there is a 75% chance of abortus, and considering the apocalyptic predictions of the present time, a justified hypothesis is presented …

Translated by Brina Beškovnik Hrastar, University graduate in translation

BIBLIOGRAPHY:

[1] Gaither, Carl C. in Cavazos-Gaither, Alma E. [2012]: Gaither's Dictionary of Scientific Quotations / Boston, MA : Springer US; 2nd ed.

[2] Barry, Robert [1998]: Teorija o skoraj vsem : (za skoraj vsakogar) : znanstveno in religiozno iskanje dokončnih odgovorov / Ljubljana : Vodnikova založba, (v Ljubljani : Dan)

[3] Čerpes, Ilka in Dešman, Miha [2007]: O urbanizmu : Kaj se dogaja s sodobnim mestom? : zbornik / Ljubljana : Krtina,

[4] Koester, Helmut; Lambdin (translator), Thomas O. (1996). "The Gospel of Thomas". In Robinson, James MacConkey. *The Nag Hammadi Library in English* (Revised ed.). Leiden, New York, Cologne: E. J. Brill.

[5] Tony Collingwood [1989]: Rarg, Laboratory, Technicolor, UK – short, animation

[6] Herbert Spencer [1971]: Structure, function and evolution / edited and with an introductory essay by Stanislav Andreski. - New York : Charles Scribner's Sons

[7] Geddes, P. [1915]: *Cities in evolution : an introduction to the town planning movement and to the study of civics* / London, Williams & Norgate

[8] MacDonald C.F. [1937]: Plato's cosmology : the Timaeus of Plato /Indianapolis, Ind. : Hackett Pub. Co.

[9] Pangeršič Irena [1998]: Upanišade / Bhavadatgita, upanišade in poezija stare Indije / [[zbrala, uredila in iz srbohrvaščine prevedla] Irena Pangeršič]. - Besedilni in slikovni podatki. - [Kranj] : [samozal.]

[10] Lilienfel'd-Toal', P.F. [1881]: *Gedanken u ber die socialwissenschaft der zukunft* / Mitau, E. Behre's Verlag

[11] Bluntschli, J.K. [1892]: *The theory of the state* /Oxford : Clarendon Press

[12] Offer, J. [2010]: *Herbert Spencer and social theory* / Houdmills, Basingstoke, Hampshire ; New York : Palgrave Macmillan

[13] Tisdale, H. [1939]: *Biology in Sociology* Vir: Social Forces Vol. 18, No.1

[14] Ideal city: Exposition Léonard de Vinci / Du 9 juin 2010 au 30 septembre 2011, le musée de Sologne va présenter le dernier projet de Léonard De Vinci and in Musee Matra on: http://www.rtvslo.si/kultura/razstave/idealno-mesto-kot-si-ga-je-zamislil-leonardo-da-vinci/235560

[15] Ellis, E.V. [2004]: *Geomantic Mathematical (re)Creation: Magic Squares and Claude Bragdon's Theosophic Architecture* / Published in Nexus V: Architecture and Mathematics

[16] Welter, V.[2002]: *Biopolis : Patrick Geddes and the city of life* /Cambridge, Mass. : MIT Press

[17] Mumford, L.[1969]: *Mesto v zgodovini* / Ljubljana :Državna založba Slovenije

[18] Mandelbrot, B.B. [1983]: *The fractal geometry of nature* / New York : W.H.Freeman

[19] Lebar Bajec, I. [2002]: Računalniški model letenja ptic v jatah : magistrska naloga / Iztok Lebar Bajec. – Ljubljana

[20] Lebar Bajec, I. [2005]: Fuzzy model for a computer simulation of bird flocking : dissertation / Iztok Lebar Bajec. - Ljubljana

[21] C.Delgado-Mata, J.Martinez, S.Bee [2007]: On the use of virtual animals with artificial fear in virtual environments, New Generation

[22] C. Hartman, N. G. Street, W. Lafayette [2006]: Autonomous Boids, Computer Animation and Virtual Worlds

[23] Pangeršič, D. [2012]: Računalniški model usklajenega pristajanja in vzletanja, diplomsko delo, Ljubljana

[24] Lebar Bajec I., Zimic N. and Mraz M., (2003), Fuzzifying the Thoughts of Animats, *Lecture Notes in Computer Science* (IFSA 2003 Conference Proceedings), submitted for review

[25] Jonathan Gray [2006]: Lost world of giants, TEACH Services, Inc.

[26] Hadith of Bukhari [1944]: Volumes I, II, III & IV, Forgotten Books

[27] Ashley, Timothy R. [1993]. The Book of Numbers. Eerdmans

[28] The HOLY Bible [1981]: containing the Old and New Testaments : revised standard version / translated from the original tongues being the version set forth a.d. 1611 revised a.d. 1881-1885 and a.d. 1901 compared with the most ancient authorities and revised a.d. 1951, 2nd ed. of the New Testament a.d. 1971. - Oxford [etc.] : Oxford University Press, [1981] (Ljubljana : Mladinska knjiga)

[29] N. Clayton Croy [2006]: The third book of Maccabees Koninklijke Brill NV Leiden The Netherlands

[30] Ralph L. Roys [1933]: The book of Chilam Balam of Chumayel, *Washington D.C..; Carnegie Institution*

[31] Perrin B. [1914]: Plutarch's lives, I.ONDON : William Heinemann, New York The Macmillan Co.

[32] Beloe W. [1806]: Herodotus I. book, London: *Primed by* We *Hansard, flear Lincoln's*-Fields

[33] Rawlinson,G. [1909]:The history Of Herodotus II., New York The Tandy-Thomas Company

[34] Rawlinson,G. [1860]:The history Of Herodotus III., New York:D. Appletox & Company, 346 & 348 Broadway.

[35] Whiston, W. [1737]: The Complete Works of Flavius Josephus, Hendrickson Pub; Updated edition 1980

[36] Ginzberg, L. [1909]: The legends of the Jews, Philadelphia, The Jewish publication society of America

[37] Jowett, B. [1953]: Aristophanes's Speech from Plato's *Symposium* translated by Benjamin Jowett from *Collected Works of Plato*, 4th Edition, Oxford U. Press

[38] Greene, B. [2005]: Tkanina vesolja, prostor, čas in tekstura resničnosti, Formatistk, Tržič

[39] Dawkins, R. [2008]: Sebični gen / [prevedel Nikolaj Pečenko]. - 1. izd. - Ljubljana : Mladinska knjiga

[40] Fikfak, A. [2004]: Evolucijske konstante naselbinske kulture v prenovi z aplikacijo na Slovenskem primorju - Goriška brda : doktorska disertacija / Alenka Fikfak ; mentor France Rihtar. - Ljubljana

Appendix
What is Erythropoiesis?

Erythropoiesis: Development and Differentiation

Elaine Dzierzak and Sjaak Philipsen

Erasmus MC, Erasmus Stem Cell Institute, Department of Cell Biology, 3000 CA Rotterdam, The Netherlands

Correspondence: e.dzierzak@erasmusmc.nl

Cold Spring Harbor Perspectives in Medicine
www.perspectivesinmedicine.org

Through their oxygen delivery function, red blood cells are pivotal to the healthy existence of all vertebrate organisms. These cells are required during all stages of life—embryonic, fetal, neonatal, adolescent, and adult. In the adult, red blood cells are the terminally differentiated end-product cells of a complex hierarchy of hematopoietic progenitors that become progressively restricted to the erythroid lineage. During this stepwise differentiation process, erythroid progenitors undergo enormous expansion, so as to fulfill the daily requirement of $\sim 2 \times 10^{11}$ new erythrocytes. How the erythroid lineage is made has been a topic of intense research over the last decades. Developmental studies show that there are two types of red blood cells—embryonic and adult. They develop from distinct hemogenic/hematopoietic progenitors in different anatomical sites and show distinct genetic programs. This article highlights the developmental and differentiation events necessary in the production of hemoglobin-producing red blood cells.

ONTOGENY OF THE HEMATOPOIETIC SYSTEM

Microscopic observations identified the first blood cells in the conceptus as those of the erythroid lineage. The early production of erythroid lineage cells occurs in the yolk sac, a transient extraembryonic tissue. These erythroid cells are nucleated and short-lived. They are derived from mesodermal cells that are formed from epiblast cells ingressing through the primitive streak (Lawson et al. 1991; Kinder et al. 1999). The newly formed mesodermal cells migrate posteriorly, enter the yolk sac, and come in close contact with endoderm cells (Fig. 1A). It is this interaction between the two cell layers that is required for the initiation of erythropoiesis (Belaoussoff et al. 1998). Interestingly, the mesodermal cells that migrate into the yolk sac form blood islands containing not only red blood cells, but also endothelial cells. The overlapping ontogenic appearance of both erythroid and endothelial cells indicates a common mesodermal precursor—the hemangioblast—with bilineage potential (Sabin 1920; Murray 1932). This is further supported by the overlap in genetic programs for the two lineages (i.e., expression of Flk-1 [KDR], Scl [Tal1], and CD34) and the lack of both lineages in embryos deficient for some of these genes (Shalaby et al. 1995; Tavian et al. 1999; Park et al. 2005). Surprisingly, hemangioblasts in vivo are localized not in the yolk sac but in the posterior primitive streak (Huber et al. 2004). As they migrate to the yolk sac, they begin their commitment to endothelial and hematopoietic progenitors, with several of these cells contributing to the formation of each blood island (Ueno and Weissman

Editors: David Weatherall, Alan N. Schechter, and David G. Nathan
Additional Perspectives on Hemoglobin and Its Diseases available at www.perspectivesinmedicine.org

 doi: 10.1101/cshperspect.a011601
Cite this article as *Cold Spring Harb Perspect Med* 2013;3:a011601

Cold Spring Harbor Perspectives in Medicine
www.perspectivesinmedicine.org

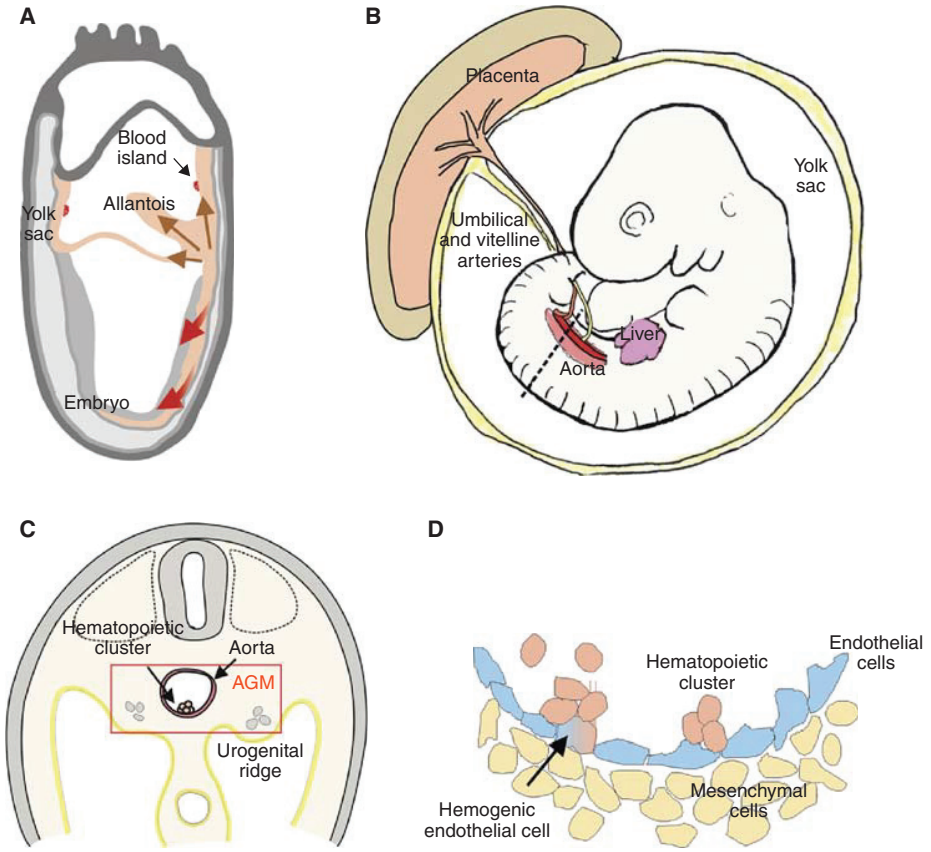


Figure 1. Ontogeny of the mouse hematopoietic system. (*A*) During gastrulation of the mouse conceptus, emerging mesodermal cells (brown arrows) migrate to the extraembryonic compartments (yolk sac and allantois). Blood islands begin to form in the yolk sac upon interactions of the mesoderm (orange) with the endoderm (gray). (Red arrows) Mesoderm migrating into the embryo proper. (*B*) Embryonic day 10.5 (E10.5) mouse embryo. Hematopoietic sites include the aorta (AGM region), yolk sac, umbilical and vitelline arteries, placenta, and liver. (Dotted line) The transverse section in panel *C*. (*C*) Transverse section showing the AGM region of an E10.5 mouse embryo. Urogenital ridges are lateral to the aorta. A hematopoietic cluster on the ventral wall of the aorta is shown. (*D*) Close-up of the aorta showing a hemogenic endothelial cell transitioning to a hematopoietic cluster cell. Nonhemogenic endothelial cells (blue) and mesenchymal cell (yellow) are shown.

2006). Yolk sac blood islands containing primitive erythrocytes are detectable in the mouse conceptus at embryonic day 7.5 (E7.5) (Russell and Bernstein 1966) and in the human conceptus at ~16–20 d of gestation (Tavian and Peault 2005).

In contrast to the rapid commitment and differentiation of primitive erythroid cells from migrating mesodermal cells, the adult erythroid lineage takes its origin from a more complex cell lineage differentiation hierarchy, with hematopoietic stem cells (HSCs) as the founder cells for this hierarchy. A cohort of rare HSCs is harbored in the bone marrow and continuously replenishes the blood system throughout adult life. To produce adult red blood cells and the many other functionally distinct lineages of differentiated blood cells, such as lymphocytes, macrophages, granulocytes, and megakaryocytes, HSCs undergo a relatively long and extensive process of cellular differentiation and proliferation. In the mouse embryos, HSCs appear 3 d later in

ontogeny than yolk sac blood islands (Muller et al. 1994; Medvinsky and Dzierzak 1996). This late appearance suggests an independent mesodermal origin for HSCs. How the adult HSC-based hierarchy develops in the embryo, and from what precursors HSCs are derived, is an important focus of developmental studies.

Again, the first clues on HSC development came from microscopic observations of a variety of developing vertebrate embryos (amphibian, avian, and mammalian). Clusters of hematopoietic cells were found within the embryo in the aorta–gonad–mesonephros (AGM) region, closely associated with the ventral lumenal aspect of the aorta (Fig. 1B–D) (for review, see Dzierzak and Speck 2008). The results of avian embryo grafting experiments performed in the mid-1970s (Dieterlen-Lievre 1975; Martin et al. 1978; Beaupain et al. 1979; Dieterlen-Lievre and Martin 1981) suggested that the development of the adult hematopoietic system begins with these clusters. Grafts of quail embryo bodies onto chick yolk sacs before vascularization revealed that the adult blood system of the chimera was quail-derived. Moreover, the embryonic aorta was found to contain hematopoietic progenitors (Cormier and Dieterlen-Lievre 1988), suggesting that this vessel is responsible for the generation of adult hematopoietic cells. Similarly, lineage-tracing experiments, in which individual blastomeres of the 32-cell stage *Xenopus* embryo were marked, showed that the blastomeres contributing to the formation of the ventral blood islands (yolk sac) are distinct from the blastomeres that contribute to the formation of the aorta, hematopoietic clusters, and pronephros (Ciau-Uitz et al. 2000). Thus, the specific localization of intrabody hematopoiesis in frog embryos has been found to be associated with the dorsal aorta and pronephros region (Turpen and Knudson 1982). These nonmammalian vertebrate embryo studies concluded that the first emergence of hematopoietic cells is in the extraembryonic yolk sac; the subsequent emergence of hematopoietic cells occurs both extraembryonically and intraembryonically; and the permanent contributors to the adult hematopoietic system are intraembryonically derived hematopoietic cells, with most extraembryonic hematopoietic cells becoming extinct. Importantly, the close association of hematopoietic cell clusters and endothelial cells on the ventral aspect of the aorta (Dieterlen-Lievre 1975) led to the hypothesis that the late-emerging, permanent adult hematopoietic system is derived from specialized "hemogenic" endothelial cells (Fig. 1D).

In contrast to the nonmammalian vertebrate species, the origin of the first HSCs in mammalian embryos was uncertain and, until the 1990s, thought to be the yolk sac (Moore and Metcalf 1970). Cell tracing studies of early stage mammalian embryos required experimental approaches different from the grafting approaches (which rely on ex utero development and large embryo size) taken in avian and amphibian embryos. One approach includes the stringent functional test for HSCs in different regions of the early/midgestation mouse conceptus—the in vivo transplantation of such cells into adult irradiated recipients. Much like adult bone marrow cell transplantations, long-term high-level self-renewing hematopoietic repopulation of adult recipients reveals the presence of HSCs in the injected cell population. Transplantation of cells from several embryonic hematopoietic tissues (yolk sac, intraembryonic AGM region, chorio-allantoic placenta, liver) showed that the first tissue to contain HSCs was the AGM (Fig. 1B,C) (Muller et al. 1994; Gekas et al. 2005; Ottersbach and Dzierzak 2005). HSCs were further localized to the aorta, vitelline, and umbilical arteries at E10.5 (de Bruijn et al. 2000). Moreover, organ explant cultures showed that the AGM region de novo produces the first adult type HSCs (Medvinsky and Dzierzak 1996). One to 1.5 d later, the mouse yolk sac, placenta, and liver also contain HSCs. Because the vascular connection between the embryo body and the extraembryonic hematopoietic sites occurs at E8.25 (Downs 1998) and the circulation carries cells between these sites, the origin of the HSCs found in these other tissues remains unknown.

The presence of hematopoietic clusters in the mouse aorta and vitelline/umbilical arteries at the time of HSC generation is intriguing (Fig. 1D). Functional studies have shown that

AGM HSCs express the same molecules (Wood et al. 1997; de Bruijn et al. 2002; North et al. 2002) as aortic hematopoietic cluster cells and, in some cases, aortic endothelial cells. Genetic (conditional knockout) studies of the Runx1 transcription factor (Chen et al. 2009) show an endothelial cell requirement for this factor in the generation of HSCs and vascular clusters, suggesting that HSCs are generated from functioning vascular endothelial cells that retain hematopoietic potential. Recent live imaging of the midgestation mouse aorta has confirmed this, clearly showing in real time the endothelial-to-hematopoietic cell transition (Boisset et al. 2010). The emerging cells are rare, localized to the ventral aspect of the aorta, and begin to express all of the expected HSC markers as they transit from a flat endothelial to a round hematopoietic morphology (Boisset et al. 2010; Yokomizo et al. 2012). Thus, HSCs are derived from endothelial cells.

With the focus on hemoglobin-producing erythrocytes—primitive erythrocytes generated early in the yolk sac and adult erythrocytes from vascular endothelial-derived HSCs—there are intermediate types of hematopoietic progenitors also generated in the embryo (Fig. 2). Before HSCs are generated at E10.5, definitive erythro-myeloid progenitors are found in the E8.5/E9 yolk sac and placenta (Alvarez-Silva et al. 2003; McGrath and Palis 2005), and multipotent (erythroid–myeloid–lymphoid) hematopoietic progenitors (Godin et al. 1995) are found in the E9 AGM, most likely in hematopoietic clusters. Tissue explant culture before progenitor assay reveals that already by E8 the

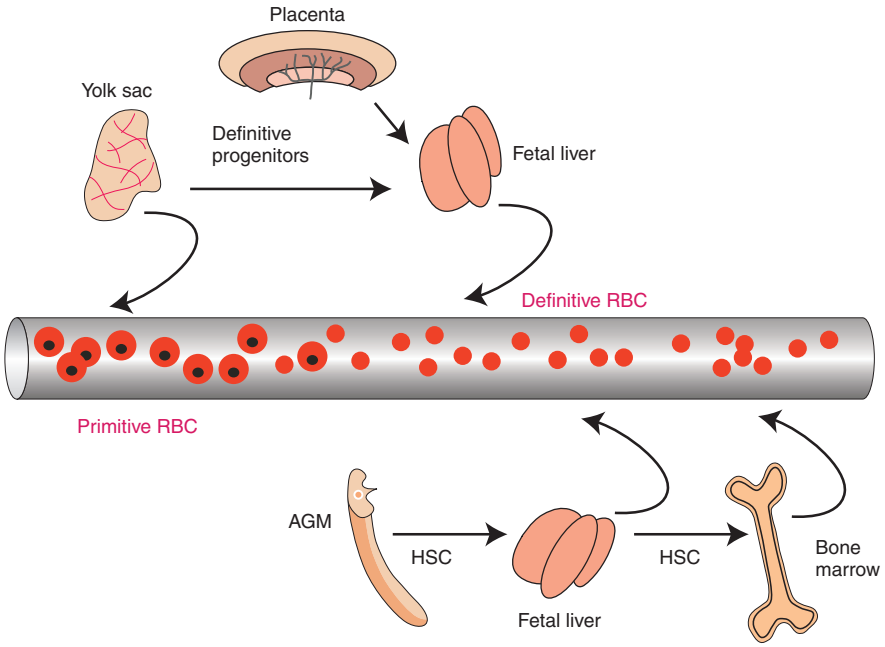


Figure 2. Ontogeny of erythroid lineage cells in the circulation. Embryonic erythrocytes (primitive red blood cells [RBCs]) are made by the yolk sac at E7.5 and are found in the circulation until ~E11/12. At E9, the yolk sac and placenta generate definitive progenitors that migrate to the fetal liver, where they differentiate to definitive RBCs (expressing fetal/adult globin) and enter the circulation. At E10.5, the AGM generates the first HSCs that migrate to the fetal liver and differentiate to the erythroid lineage (among other lineages), and these definitive RBCs enter the circulation. Fetal liver HSCs migrate and colonize the bone marrow at birth, where they provide lifelong production of definitive RBCs for the circulation. The spleen also is a site of differentiation for erythroid cells (not shown).

yolk sac, AGM, and allantois (Cumano et al. 1996; Zeigler et al. 2006; Corbel et al. 2007) contain cells with hemogenic potential. Interestingly, in the absence of circulation in *Ncx1*$^{-/-}$ embryos (heartbeat defect), the numbers of erythro-myeloid progenitors in the yolk sac were found to be equivalent to the cumulative number of progenitors in wild-type embryos in all anatomic sites (Lux et al. 2007). No progenitors were found in the *Ncx1*$^{-/-}$ AGM, suggesting that the yolk sac normally generates all of these progenitors and distributes them to other tissues. As the cells colonize the liver, the newly emigrated progenitors expand and differentiate toward the definitive erythroid lineage (Ema and Nakauchi 2000).

ERYTHROID LINEAGE DIFFERENTIATION DURING ONTOGENY

Primitive erythrocytes, emerging in the extra-embryonic yolk sac, are relatively large cells. The primitive cells are characterized by the expression of embryonic globins (εy, βh1, and ζ in the mouse; ε, γ, and ζ in man), which form a variety of distinguishable hemoglobin tetramers in man ($\zeta_2\varepsilon_2$ [Gower1], $\alpha_2\varepsilon_2$ [Gower2], $\zeta_2\gamma_2$ [Portland1], $\zeta_2\beta_2$ [Portland2]). In mammals, these are the only erythroid cells that retain their nucleus when they enter the circulation. Once released in the bloodstream, the macrocytic primitive erythrocytes retain proliferative capacity, and mitotic figures are observed in the circulating blood of early mammalian embryos (Lin et al. 1996). Intravascular erythropoiesis is not normally observed at any other developmental stage. The long-held view that primitive erythrocytes remain nucleated and that they disappear from the circulation very quickly during the embryonic-to-fetal transition period has been recently revised. In fact, primitive cells enucleate very efficiently between E12.5 and E14.5, resulting in macrocytic, enucleated erythrocytes (Fraser et al. 2007). Beginning at E11.5, newly emigrating erythro-myeloid progenitors (and subsequently HSCs) differentiate in the fetal liver to produce the first definitive erythrocytes (Fig. 2). There is an immediate switch to fetal/adult globins when definitive erythropoiesis starts in the fetal liver. Expression of a specific fetal β-like globin (γ-globin) is a feature of anthropoid primates. Hemoglobin tetramers consisting of α- and γ-globin chains ($\alpha_2\gamma_2$) are known as HbF in humans. These hemoglobins allow the developing fetus to extract oxygen more efficiently from the maternal blood. Mammalian definitive erythrocytes expel their nucleus before they enter the circulation and are smaller in size than primitive erythrocytes.

Around the time of birth, the site of erythropoiesis switches to the bone marrow and the spleen. Humans rely mainly on the bone marrow for steady-state adult erythropoiesis, but in mice the spleen remains an important erythropoietic organ during adult life. Under erythroid stress conditions, for example, low oxygen pressure or anemia, the spleen of both mouse and man is used to expand the erythropoietic capacity (Socolovsky 2007).

Fetal globin expression is silenced in adult erythropoiesis. Hemoglobin tetramers composed of α- and β-globin ($\alpha_2\beta_2$, HbA1) account for ~97% of all hemoglobin in adult erythrocytes. HbA2 ($\alpha_2\delta_2$) and HbF account, respectively, for ~2% and ~1% of total hemoglobin in most adults. High HbF is restricted to a few cells, termed F cells, in normal adults (Boyer et al. 1975). Clonal analysis has shown that F cells are derived from the same progenitor cells as the cells containing adult globin, ruling out that fetal and adult stem cell lineages coexist (Papayannopoulou et al. 1977). Some individuals maintain higher levels of HbF throughout adult life. This condition, known as hereditary persistence of fetal hemoglobin (HPFH), is caused in the majority of cases by deletions in the β-globin locus, but also by point mutations in the γ-globin gene promoters (Stamatoyannopoulos 2005). In rare cases, the HPFH phenotype does not segregate with the β-globin locus, suggesting a *trans*-regulatory mechanism (see also Sankaran and Orkin 2013). The HPFH condition is not clinically manifest, but it is a factor ameliorating the effects of β-thalassemia and sickle cell disease. Reactivation of γ-globin expression in adults with these disorders is therefore a very attractive therapeutic approach,

because the large majority of patients will have normal γ-globin genes that they have switched off after birth. Despite the fact that mice do not have a fetal β-like globin gene, the γ-globin genes in human β-globin locus transgenes are expressed in the early fetal liver and silenced subsequently in development between E13.5 and E14.5 (Dillon and Grosveld 1991; Strouboulis et al. 1992). Furthermore, γ-globin transgenes with HPFH mutations in the promoter phenocopy the HPFH condition in mice (Berry et al. 1992; Peterson et al. 1995).

ERYTHROID DIFFERENTIATION WITHIN THE ADULT HEMATOPOIETIC HIERARCHY

Erythroid cells are derived from HSCs, but the differentiation path they follow is still a matter of debate (Fig. 3) (Buza-Vidas et al. 2007). Immature progenitors are capable of giving rise to multilineage colonies, but whether there is a fixed order to cell fate decisions (i.e., at each stage a cell has limited choices) or whether there is greater plasticity to a cell's potential fates remains to be resolved. The classical model, put forward by the Weissman group, posits a decision between two fates at each step in differentiation, thereby gradually diminishing lineage potential (Fig. 3). More recently, an alternative scheme proposed by Adolfsson et al. (2005) identified a highly proliferative lymphoid-primed multipotent progenitor (LMPP) with GM potential but devoid of the ability to adopt erythroid or megakaryocytic lineage fates (Fig. 3, dotted arrows).

Cell populations corresponding to these progenitors can be purified by flow cytometric sorting based on the expression of various cell surface markers. Lineage output of these cells is determined by the mature differentiated cells emerging in colony assays in response to growth factors. Immature erythroid-restricted progenitors are identified as the burst forming unit-erythroid (BFU-E), so-called because its earliest progeny are motile, giving rise to a multi-subunit colony (or burst). These large colonies containing up to several thousand hemoglobinized cells appear after 5–8 d (mouse) or 10–14 d (human) in methylcellulose cultures. Their growth is dependent on several factors, the most important of which are stem cell factor (SCF), thrombopoietin (TPO), interleukin 3 (IL3), IL11, and FLT3-ligand. BFU-E occurs at a frequency of $40–120/10^5$ bone marrow cells and also circulates in the peripheral blood at a frequency of $10–40/10^5$ light-density mononuclear cells (Migliaccio et al. 2001).

More mature erythroid progenitors, colony-forming units-erythroid (CFU-E), consist of small colonies of 16–125 cells that appear after 2–3 d (mouse) or 5–8 d (human) in methylcellulose culture. They are fivefold to eightfold more abundant than BFU-E in bone marrow and under normal circumstances do not appear in the circulation. As progenitors undergo the differentiation process, their numbers increase, with their proliferative potential simultaneously decreasing.

Several techniques have been described for the production of erythroblasts in liquid cultures (Fibach et al. 1989; Dolznig et al. 2001; Migliaccio et al. 2002). Although culture conditions differ in each protocol, SCF, erythropoietin (EPO), dexamethasone (Dex), and transferrin are commonly present, usually supplemented by insulin or IGF-1. In adult peripheral blood, the majority of the in vitro erythroid expansion potential resides in $CD34^-$ cells (van den Akker et al. 2010). These liquid cultures are advantageous for producing large numbers of erythroblasts from peripheral blood samples, thus enabling functional analyses of normal or abnormal erythropoiesis without the need for bone marrow sampling. In addition, erythroid cultures can also be obtained using mouse or human embryonic stem cells as the starting material (Carotta et al. 2004; Pilat et al. 2005; Olivier et al. 2006), and large-scale production of fully matured human erythrocytes has been reported (Neildez-Nguyen et al. 2002; Giarratana et al. 2005). The advent of induced pluripotent stem (iPS) cells raises prospects for production of patient-specific erythrocytes for transfusion purposes. However, at present, it is prohibitively expensive and a daunting task to generate the vast numbers of cells required for clinical practice (Douay and Andreu 2007; see also Arora and Daley 2012).

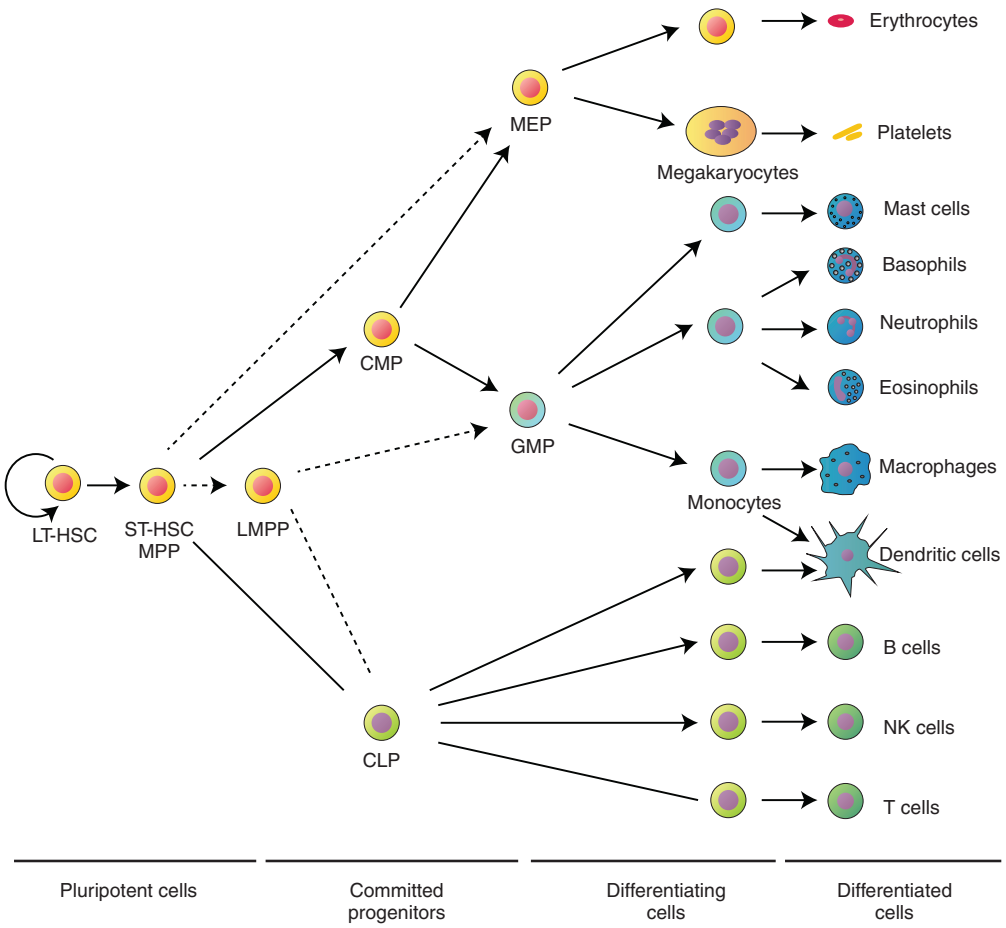


Figure 3. Proposed models for the hematopoietic hierarchy. In the model proposed by the Weissman group (Kondo et al. 1997; Akashi et al. 2000; Manz et al. 2002) (solid arrows), multipotential progenitors (MPPs or short-term HSCs [ST-HSCs]) give rise to either a common lymphocyte progenitor (CLP) or a common myeloid progenitor (CMP), which, in turn, gives rise to either a granulocyte-macrophage progenitor (GMP, equivalent to CFU-GM) or a megakaryocyte-erythroid progenitor (MEP). The alternate model suggested by the Jacobson group (Adolfsson et al. 2005) (dotted arrows) involves the generation of MEPs directly from the MPPs/ST-HSCs, whereas a lymphoid-primed multipotential progenitor (LMPP) has the potential to generate both CLPs and GMPs. LT-HSC, Long-term hematopoietic stem cell; NK cell, natural killer cell. (This figure is modified from data by Ferreira et al. 2005; reprinted, with permission, from the author as defined by the American Society for Microbiology.)

ERYTHROPOIESIS: REGULATION AND NICHE

Erythrocytes represent the most common cell type in adult blood. Human blood contains ~5 × 10^6 erythrocytes per microliter (normal range 4.7 × 10^6 to 6.1 × 10^6 for males and 4.2 × 10^6 to 5.4 × 10^6 for females); these cells have an average life span of 120 d. New erythrocytes are constantly produced in the bone marrow, which provides a niche consisting of endothelial cells of the vascular system, osteoblasts, stromal cells, hematopoietic cells, and the extracellular matrix. This complex niche supports direct cell–cell contact and exposure of the developing hematopoietic cells to cell adhesion molecules,

growth factors, and cytokines. The earliest erythroid progenitors are responsive to cytokines including TPO, GM-CSF, IL3, and IL11, and in particular to SCF. SCF binds to its receptor KIT, a tyrosine kinase that signals through several pathways including PI-3 kinase, Src kinases, and PLC-γ. At subsequent stages, SCF acts synergistically with EPO in the proliferation and expansion of the developing erythroid progenitors and may play a role in phosphorylating the EPO receptor itself (Wu et al. 1995; see Bunn 2013). Erythroid cells at the terminal stages of differentiation have shed their nucleus, endoplasmic reticulum, and mitochondria, and, consequently, they are no longer able to proliferate. To maintain the red blood cell count in the ~5 L of blood of an adult individual, ~2.4 $\times 10^6$ new erythrocytes have to be produced each second. The new cells enter the circulation as reticulocytes that are still engaged in protein translation. In humans, it takes ~1 wk for reticulocytes to complete the maturation process. In the bone marrow, a series of intermediate erythroid precursors can be recognized that progressively gains erythroid characteristics (Fig. 4). Development from the pro-erythroblast to the reticulocyte involves four to five rapid cell divisions, resulting in a progressive reduction in cell size. Mature erythrocytes have a diameter of only 6–8 μm. Their small size and biconcave shape creates a large surface area for gas exchange and allows the cells to enter the microcapillaries in the tissues.

Under steady-state conditions, ~1% of the erythrocytes are cleared every day and replaced by new cells. Remarkably, the rate of erythropoiesis can increase significantly from this baseline level in response to hypoxic stress, which occurs when adequate oxygen supply to all tissues is compromised by insufficient numbers of functional erythrocytes. Increasing red cell production is the primary response to counteract hypoxic stress. EPO production in the kidneys is directly regulated by tissue oxygen tension through the activity of the hypoxia-inducible transcription factor complex. Although EPO is the main regulator of red cell production (see Bunn 2013), other factors have an auxiliary role in the expansion of the erythroid progenitor compartment through their support of progenitor self-renewal. In particular, bone morphogenetic protein 4 (BMP4)/SMAD5 (Lenox et al. 2005), STAT5 (Socolovsky et al. 2001), SCF/KIT (Menon et al. 2006), and the glucocorticoid receptor (GR) (Bauer et al. 1999) are known to be involved.

A decreased apoptotic rate of erythroid progenitors may also contribute to the increase in red cell production that occurs under erythropoietic stress. It is believed that under steady-state conditions up to 60% of pro-erythroblasts succumb to apoptosis in the mouse spleen (Liu

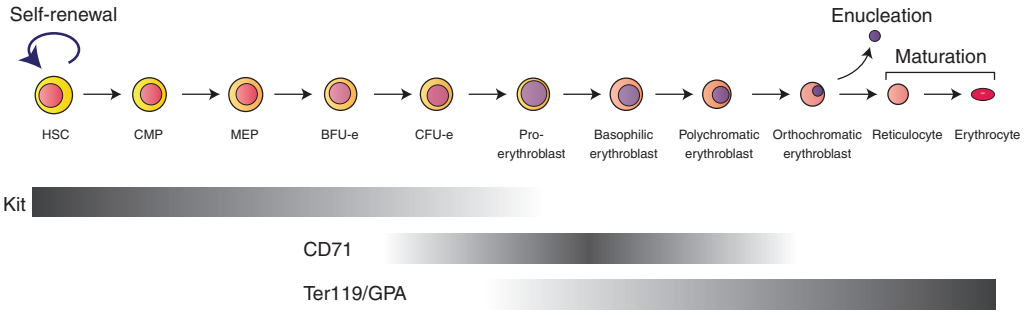


Figure 4. Erythroid differentiation in the mouse. The expression of the most commonly used cell surface markers to identify the various stages is indicated by the bars. Cells at the CFU-e and pro-erythroblast stage are the most sensitive to, and dependent on, the presence of EPO. Gray, low expression; black, high expression; HSC, hematopoietic stem cell; CMP, common myeloid progenitor; MEP, megakaryocyte-erythroid progenitor; BFU-e, burst-forming unit, erythroid; CFU-e, colony-forming unit, erythroid.

et al. 2006). Mice deficient for the STAT5 transcription factor, the major downstream signaling target of EPOR, have a blunted stress erythropoietic response. The erythroid progenitors have an increased rate of apoptosis attributed to their failure to up-regulate expression of the antiapopotic BCL-X_L protein (Socolovsky et al. 1999, 2001). Furthermore, the FAS/FASL death receptor/death ligand system has been proposed to regulate erythroid homeostasis (De Maria et al. 1999). Under stress conditions, expression of FAS and FASL is reduced in erythroid cells and could contribute to the enhanced survival of these cells, further indicating that the survival function of the EPOR/STAT5 pathway is an important modulator of the erythropoietic rate (Liu et al. 2006).

ERYTHROBLASTIC ISLANDS ARE STRUCTURAL UNITS OF TERMINAL ERYTHROID DIFFERENTIATION

The erythroblastic island is a structural unit in the bone marrow where terminal erythroid differentiation takes place (Bessis 1958). It consists of a central macrophage (also known as the nurse cell) surrounded by differentiating erythroid progenitors (Fig. 5). Erythroblastic islands are also found in the mouse fetal liver (Fig. 5), but a role for an analogous structure has not been identified in the yolk sac. The fact that yolk sac cells enter the circulation without undergoing enucleation, a process in which the macrophage plays an important role, supports the notion that primitive erythropoiesis does not require the formation of islands. However, macrophages are formed during primitive hematopoiesis, and further investigations are necessary to determine the role of these cells in primitive erythropoiesis.

Several proteins on the surface of the macrophage and the erythroblasts mediate interactions between the macrophage and erythroblasts, and between the erythroblasts themselves. The erythroblast-macrophage protein (EMP or macrophage-erythroblast attacher MAEA) is expressed on both cell types and mediates adhesion between the cells. MAEA knockout mice survive until birth, displaying defects in terminal erythroid maturation (Soni et al. 2006). Formation of erythroblastic islands is impaired and MAEA-null macrophages appear to lack the extensive cytoplasmatic extensions typical of mature macrophages. MAEA-null macrophages are unable to interact with wild-type erythroblasts. In contrast, MAEA-null erythroblasts can interact with wild-type macrophages, but this does not rescue the enucleation defect of these erythroblasts. In enucleating wild-type erythroblasts, MAEA colocalizes with F-actin aggregates present at the constriction between the extruding nucleus and the reticulocyte. The actin cytoskeleton in MAEA-null erythroblasts is predominantly localized to the cell membrane,

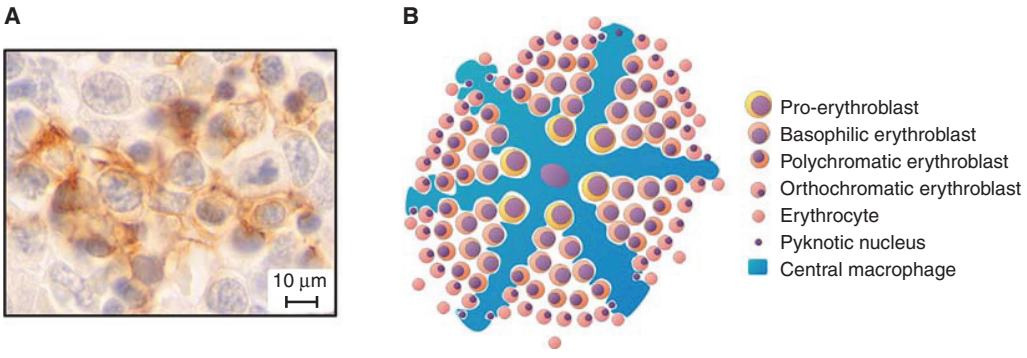


Figure 5. The erythroblastic island. (*A*) Erythroblastic island in E13.5 fetal liver. The cytoplasmic extensions of the central macrophage (stained with the F4/80 antibody) (brown) are surrounding erythroid cells at various stages of differentiation. (*B*) Schematic drawing of an erythroblastic island.

and very little cytoplasmic actin is observed. Collectively, it can be concluded that MAEA is required for the organization of the erythroblastic island and for efficient enucleation of erythroblasts.

The role of other cell adhesion molecules and interactions with extracellular matrix proteins such as laminin and fibronectin is less clearly defined. Erythroblasts express α_4 (Itga4)/CD29/β_1 integrin (Itgb1), and the CD242 (Icam4, LW blood group) counter-receptor. Macrophages express CD51 (α_v integrin, Itgav) and the vascular cell adhesion molecule 1 (Vcam1) counter-receptor. Perturbation of the integrin system can adversely affect erythroblastic island formation (Lee et al. 2006) and stress erythropoiesis (Scott et al. 2003), but the generic role of cell adhesion in tissue integrity and the considerable potential for redundancy preclude the assignment of specific functions to individual factors.

A role for signaling between erythroid cells has been most convincingly shown for death ligand/death receptor interactions. Erythroid cells express the CD95 (FAS) death receptor throughout differentiation. Only mature cells express the ligand CD95L (FASL), but these cells are insensitive to FAS signaling. In contrast, immature cells activate proapoptotic proteases in response to FASL exposure. The levels of the essential transcription factors TAL1 and GATA1 are reduced through cleavage by activated caspases, most notably by caspase 3 (CASP3) (De Maria et al. 1999; Zeuner et al. 2003; Ribeil et al. 2007). This will stop progression along the erythroid differentiation pathway and may induce cell death. A decreased survival rate of erythroid progenitor cells is a hallmark of many acquired and hereditary anemias. Patients with rheumatoid arthritis develop anemia in ~50% of cases, and treatment with a blocking antibody directed against the death receptor ligand TNFα improved the anemia and decreased the elevated numbers of apoptotic erythroid progenitors in the bone marrow (Papadaki et al. 2002). An increased rate of apoptosis is also observed in β-thalassemia patients. This results in a phenomenon known as ineffective erythropoiesis (Centis et al. 2000; Mathias et al. 2000; Pootrakul et al. 2000; Papadaki et al. 2002). Up to 80% of erythroid progenitors may be lost because of apoptosis occurring at the polychromatic erythroblast stage (Mathias et al. 2000). The apoptotic erythroblasts are cleared very rapidly by macrophages. These cells are activated by increased interferon-γ (IFNG) levels in approximately one-third of the patients (Wanachiwanawin et al. 1999), and this may contribute to the quantitative differences in ineffective erythropoiesis between different patients. In addition, many inflammatory diseases are accompanied by anemia, and in a mouse model, IFNG has been implicated in anemia of chronic disease by activating macrophages, reducing erythrocyte life span and inhibiting erythropoiesis (Libregts et al. 2011).

In normal erythropoiesis, expelled nuclei are phagocytosed very rapidly by the central macrophages. Once released, the nuclei contain very low levels of ATP and start to expose phosphatidylserine on their surface, because it requires energy to maintain phosphatidylserine exclusively localized to the inner leaflet of the cell membrane. Surface exposure of phosphatidylserine is an early event in apoptosis and serves as an "eat me" signal for apoptotic cells. This signal is also used for the engulfment of expelled nuclei by the macrophages (Yoshida et al. 2005).

TRANSCRIPTIONAL REGULATION OF ERYTHROPOIESIS AND THE STEM CELL/EARLY PROGENITOR COMPARTMENT

A wide variety of transcription factors is involved in the establishment of hematopoietic cell lineages. For example, TAL1, a basic helix–loop–helix transcription factor, and LMO2, an LIM-domain transcription factor, are critical for the onset of hematopoiesis because null embryos show complete absence of primitive and definitive hematopoiesis (Robb et al. 1995, 1996; Shivdasani et al. 1995; Porcher et al. 1996). The zinc-finger transcription factor GATA2 is also essential for the early stages of hematopoiesis. Primitive and definitive hematopoiesis is abrogated when the GATA2 gene is deleted, and it appears to play a role in the proliferation of the early precursors rather than in

their differentiation (Tsai et al. 1994; Tsai and Orkin 1997). RUNX1 is crucial for the early stages of definitive hematopoiesis. In RUNX1-null embryos, yolk sac hematopoiesis is normal but fetal liver hematopoiesis is absent (Okuda et al. 1996).

Once multipotent progenitors arise from the HSC and proliferate, the process of lineage restriction starts. The first step in this process involves restriction to either the myeloid or the lymphoid lineage. Transcription factors that are preferentially expressed in cells destined to one of those fates have been identified, but few have been extensively studied. PU.1, a member of the Ets family of transcription factors, is the best-studied transcription factor known to be involved in lineage restriction at this stage. PU.1's effect on lineage commitment is dependent on its expression level. A high level of expression leads to commitment to the myeloid lineage, whereas lower levels of expression lead to commitment to the lymphoid lineage (Scott et al. 1994; Nerlov and Graf 1998; Huang et al. 2007). Thus, owing to their role in the stem cell/progenitor compartment, inactivation of these factors also affects erythropoiesis.

Because the number of transcription factors with identifiable functions specifically during erythropoiesis is too vast to allow a thorough discussion of each, we will focus on KLF1. This transcription factor is required for terminal erythroid differentiation and provides one of the best-studied examples of an erythroid transcriptional regulator. Expression of the KLF1 (formerly known as erythroid Krüppel-like factor [EKLF]) is largely restricted to the erythroid cell lineage (Southwood et al. 1996). KLF1 specifically binds the sequence 5′-CCACACCCT-3′ (Miller and Bieker 1993). β-Thalassemia patients that carry mutations in the KLF1 binding site in the β-globin promoter display strongly reduced expression of β-globin (Orkin et al. 1984; Feng et al. 1994; Faustino et al. 1996). The role of KLF1 has been studied extensively in mice (Nuez et al. 1995; Perkins et al. 1995). Mice heterozygous for the KLF1 gene appear completely healthy. In the absence of KLF1, however, the fetuses develop a fatal anemia and die around E14. The primitive erythroid cells function sufficiently for normal survival of the KLF1 knockout embryos up to ~E12. Embryonic globin gene expression is not influenced by the absence of KLF1, even though KLF1 normally binds these genes in vivo (Zhou et al. 2006). When the embryos switch to definitive erythropoiesis in the fetal liver, KLF1-null mutants rapidly develop anemia because of a deficit in β-globin expression. Remarkably, the number of CFU-E in the KLF1-null fetal livers is similar to those found in wild-type fetal livers, showing that KLF1 deficiency causes a very late erythroid defect (Nuez et al. 1995; Perkins et al. 1995). Furthermore, fetal liver-derived erythroid cells of $KLF1^{-/-}$ fetuses have an abnormal morphology, and most of the cells retain a nucleus, indicating that the adult β-globin genes are not the only target genes of KLF1. Indeed, $KLF1^{-/-}$ mice could not be rescued by expression of exogenous human γ-globin (Perkins et al. 2000). Genome-wide expression analyses of $KLF1^{-/-}$ erythroid cells showed that KLF1 activates many other erythroid-specific genes, including genes encoding proteins associated with the erythroid cell membrane, such as band 4.9/dematin. These proteins are important for the function and stability of the erythrocytes. In addition, KLF1 has a role in cell cycle regulation linked to the proliferation arrest required for terminal differentiation (Tallack et al. 2007). Thus, KLF1 is an activator of essential erythroid genes that are up-regulated during terminal erythroid differentiation.

The first reported loss-of-function mutations in human KLF1 were linked to the rare blood group In(Lu) (inhibitor of Lutheran antigen expression) and always occurred in the presence of a normal KLF1 allele. Gene expression profiling identified more than 650 putative KLF1 target genes, including the blood group antigens BCAM and CD44, which are suppressed in the In(Lu) individuals (Singleton et al. 2008). A study of a large Maltese pedigree concluded that haploinsufficiency for KLF1 causes HPFH. All carriers displayed high HbF levels, although with considerable variation (mean 8.4%; range 3.3%–19.5%) (Borg et al. 2010). Part of this variability could be explained by SNP haplotypes at the *BCL11A*locus (Menzel

et al. 2007), which encodes a repressor of γ-globin expression (Sankaran et al. 2008). Importantly, KLF1 was shown to be a direct activator of BCL11A expression (Borg et al. 2010; Zhou et al. 2010). Therefore, attenuation of KLF1 activity could be a fruitful approach to raise HbF levels in patients with β-type hemoglobinopathies. Supporting this notion, a sickle cell anemia patient with KLF1 haploinsufficiency was reported recently (Gallienne et al. 2012). This patient displayed a high HbF level (20.3%) and had a particularly mild disease phenotype. In contrast, missense mutations of critical residues in the DNA binding domain of KLF1 can have a dominant phenotype with severe consequences. Two unrelated patients with congenital dyserythropoietic anemia (CDA) carried a missense mutation (p.E325K) in the DNA-binding domain of KLF1. Although the patients displayed very high levels of HbF (31.6% and 44%), this mutation had a dominant effect that resulted in severe hemolytic anemia (Arnaud et al. 2010). Given the broad impact of KLF1 on erythroid-specific gene expression (Drissen et al. 2005; Pilon et al. 2008; Singleton et al. 2008; Borg et al. 2010), the array of human erythroid phenotypes associated with KLF1 mutations will likely be expanded as more cases are described in detail. This is illustrated by two recent studies reporting that zinc protoporphyria (Perseu et al. 2011) and increased HbA2 levels (Perseu et al. 2011) are linked to KLF1 mutations.

CONCLUDING REMARKS

In conclusion, much progress has been made in understanding the ontogeny, expansion, and terminal differentiation of erythroid cells, and future work will contribute to the ultimate goal of fully comprehending the molecular control of erythropoiesis at the systems level.

ACKNOWLEDGMENTS

We acknowledge support from the Landsteiner Society for Blood Research, Netherlands Institute for Regenerative Medicine FES subsidy, National Institutes of Health R37 DK54077, Netherlands Organization for Scientific Research (NWO), and Netherlands Genomics Initiative (NGI).

REFERENCES

*Reference is also in this collection.

Adolfsson J, Mansson R, Buza-Vidas N, Hultquist A, Liuba K, Jensen CT, Bryder D, Yang L, Borge OJ, Thoren LA, et al. 2005. Identification of $Flt3^+$ lympho-myeloid stem cells lacking erythro-megakaryocytic potential. *Cell* **121:** 295–306.

Akashi K, Traver D, Miyamoto T, Weissman IL. 2000. A clonogenic common myeloid progenitor that gives rise to all myeloid lineages. *Nature* **404:** 193–197.

Alvarez-Silva M, Belo-Diabangouaya P, Salaun J, Dieterlen-Lievre F. 2003. Mouse placenta is a major hematopoietic organ. *Development* **130:** 5437–5444.

Arnaud L, Saison C, Helias V, Lucien N, Steschenko D, Giarratana MC, Prehu C, Foliguet B, Montout L, de Brevern AG, et al. 2010. A dominant mutation in the gene encoding the erythroid transcription factor KLF1 causes a congenital dyserythropoietic anemia. *Am J Hum Genet* **87:** 721–727.

* Arora N, Daley GQ. 2012. Pluripotent stem cells in research and treatment of hemoglobinopathies. *Cold Spring Harb Perspect Med* **2:** a011841.

Bauer A, Tronche F, Wessely O, Kellendonk C, Reichardt HM, Steinlein P, Schutz G, Beug H. 1999. The glucocorticoid receptor is required for stress erythropoiesis. *Genes Dev* **13:** 2996–3002.

Beaupain D, Martin C, Dieterlen-Lievre F. 1979. Are developmental hemoglobin changes related to the origin of stem cells and site of erythropoiesis? *Blood* **53:** 212–225.

Belaoussoff M, Farrington SM, Baron MH. 1998. Hematopoietic induction and respecification of A-P identity by visceral endoderm signaling in the mouse embryo. *Development* **125:** 5009–5018.

Berry M, Grosveld F, Dillon N. 1992. A single point mutation is the cause of the Greek form of hereditary persistence of fetal haemoglobin. *Nature* **358:** 499–502.

Bessis M. 1958. L'ilot erythroblastique, unite fonctionnelle de la moelle osseuse. *Rev Hematol* **13:** 8–11.

Boisset JC, van Cappellen W, Andrieu-Soler C, Galjart N, Dzierzak E, Robin C. 2010. In vivo imaging of haematopoietic cells emerging from the mouse aortic endothelium. *Nature* **464:** 116–120.

Borg J, Papadopoulos P, Georgitsi M, Gutierrez L, Grech G, Fanis P, Phylactides M, Verkerk AJ, van der Spek PJ, Scerri CA, et al. 2010. Haploinsufficiency for the erythroid transcription factor KLF1 causes hereditary persistence of fetal hemoglobin. *Nat Genet* **42:** 801–805.

Boyer SH, Belding TK, Margolet L, Noyes AN. 1975. Fetal hemoglobin restriction to a few erythrocytes (F cells) in normal human adults. *Science* **188:** 361–363.

* Bunn HF. 2013. Erythropoietin. *Cold Spring Harb Perspect Med* doi: 10.1101/cshperspect.a011619.

Buza-Vidas N, Luc S, Jacobsen SE. 2007. Delineation of the earliest lineage commitment steps of haematopoietic

stem cells: New developments, controversies and major challenges. *Curr Opin Hematol* **14:** 315–321.

Carotta S, Pilat S, Mairhofer A, Schmidt U, Dolznig H, Steinlein P, Beug H. 2004. Directed differentiation and mass cultivation of pure erythroid progenitors from mouse embryonic stem cells. *Blood* **104:** 1873–1880.

Centis F, Tabellini L, Lucarelli G, Buffi O, Tonucci P, Persini B, Annibali M, Emiliani R, Iliescu A, Rapa S, et al. 2000. The importance of erythroid expansion in determining the extent of apoptosis in erythroid precursors in patients with β-thalassemia major. *Blood* **96:** 3624–3629.

Chen MJ, Yokomizo T, Zeigler BM, Dzierzak E, Speck NA. 2009. Runx1 is required for the endothelial to haematopoietic cell transition but not thereafter. *Nature* **457:** 887–891.

Ciau-Uitz A, Walmsley M, Patient R. 2000. Distinct origins of adult and embryonic blood in *Xenopus*. *Cell* **102:** 787–796.

Corbel C, Salaun J, Belo-Diabangouaya P, Dieterlen-Lievre F. 2007. Hematopoietic potential of the pre-fusion allantois. *Dev Biol* **301:** 478–488.

Cormier F, Dieterlen-Lievre F. 1988. The wall of the chick embryo aorta harbours M-CFC, G-CFC, GM-CFC and BFU-E. *Development* **102:** 279–285.

Cumano A, Dieterlen-Lievre F, Godin I. 1996. Lymphoid potential, probed before circulation in mouse, is restricted to caudal intraembryonic splanchnopleura. *Cell* **86:** 907–916.

de Bruijn MF, Speck NA, Peeters MC, Dzierzak E. 2000. Definitive hematopoietic stem cells first develop within the major arterial regions of the mouse embryo. *EMBO J* **19:** 2465–2474.

de Bruijn MF, Ma X, Robin C, Ottersbach K, Sanchez MJ, Dzierzak E. 2002. Hematopoietic stem cells localize to the endothelial cell layer in the midgestation mouse aorta. *Immunity* **16:** 673–683.

De Maria R, Zeuner A, Eramo A, Domenichelli C, Bonci D, Grignani F, Srinivasula SM, Alnemri ES, Testa U, Peschle C. 1999. Negative regulation of erythropoiesis by caspase-mediated cleavage of GATA-1. *Nature* **401:** 489–493.

Dieterlen-Lievre F. 1975. On the origin of haemopoietic stem cells in the avian embryo: An experimental approach. *J Embryol Exp Morphol* **33:** 607–619.

Dieterlen-Lievre F, Martin C. 1981. Diffuse intraembryonic hemopoiesis in normal and chimeric avian development. *Dev Biol* **88:** 180–191.

Dillon N, Grosveld F. 1991. Human γ-globin genes silenced independently of other genes in the β-globin locus. *Nature* **350:** 252–254.

Dolznig H, Boulme F, Stangl K, Deiner EM, Mikulits W, Beug H, Mullner EW. 2001. Establishment of normal, terminally differentiating mouse erythroid progenitors: Molecular characterization by cDNA arrays. *FASEB J* **15:** 1442–1444.

Douay L, Andreu G. 2007. Ex vivo production of human red blood cells from hematopoietic stem cells: What is the future in transfusion? *Transfus Med Rev* **21:** 91–100.

Downs KM. 1998. The murine allantois. *Curr Top Dev Biol* **39:** 1–33.

Drissen R, von Lindern M, Kolbus A, Driegen S, Steinlein P, Beug H, Grosveld F, Philipsen S. 2005. The erythroid phenotype of EKLF-null mice: Defects in hemoglobin metabolism and membrane stability. *Mol Cell Biol* **25:** 5205–5214.

Dzierzak E, Speck NA. 2008. Of lineage and legacy: The development of mammalian hematopoietic stem cells. *Nat Immunol* **9:** 129–136.

Ema H, Nakauchi H. 2000. Expansion of hematopoietic stem cells in the developing liver of a mouse embryo. *Blood* **95:** 2284–2288.

Faustino P, Lavinha J, Marini MG, Moi P. 1996. β-Thalassemia mutation at −90C → T impairs the interaction of the proximal CACCC box with both erythroid and non-erythroid factors. *Blood* **88:** 3248–3249.

Feng WC, Southwood CM, Bieker JJ. 1994. Analyses of β-thalassemia mutant DNA interactions with erythroid Kruppel-like factor (EKLF), an erythroid cell-specific transcription factor. *J Biol Chem* **269:** 1493–1500.

Ferreira R, Ohneda K, Yamamoto M, Philipsen S. 2005. GATA1 function, a paradigm for transcription factors in hematopoiesis. *Mol Cell Biol* **25:** 1215–1227.

Fibach E, Manor D, Oppenheim A, Rachmilewitz EA. 1989. Proliferation and maturation of human erythroid progenitors in liquid culture. *Blood* **73:** 100–103.

Fraser ST, Isern J, Baron MH. 2007. Maturation and enucleation of primitive erythroblasts during mouse embryogenesis is accompanied by changes in cell-surface antigen expression. *Blood* **109:** 343–352.

Gallienne AE, Dreau HM, Schuh A, Old J, Henderson S. 2012. Ten novel mutations in the erythroid transcription factor KLF1 gene associated with increased fetal hemoglobin levels in adults. *Haematologica* **97:** 340–343.

Gekas C, Dieterlen-Lievre F, Orkin SH, Mikkola HK. 2005. The placenta is a niche for hematopoietic stem cells. *Dev Cell* **8:** 365–375.

Giarratana MC, Kobari L, Lapillonne H, Chalmers D, Kiger L, Cynober T, Marden MC, Wajcman H, Douay L. 2005. Ex vivo generation of fully mature human red blood cells from hematopoietic stem cells. *Nat Biotechnol* **23:** 69–74.

Godin I, Dieterlen-Lievre F, Cumano A. 1995. Emergence of multipotent hemopoietic cells in the yolk sac and paraaortic splanchnopleura in mouse embryos, beginning at 8.5 days postcoitus. *Proc Natl Acad Sci* **92:** 773–777.

Huang G, Zhang P, Hirai H, Elf S, Yan X, Chen Z, Koschmieder S, Okuno Y, Dayaram T, Growney JD, et al. 2007. PU.1 is a major downstream target of AML1 (RUNX1) in adult mouse hematopoiesis. *Nat Genet* **40:** 51–60.

Huber TL, Kouskoff V, Fehling HJ, Palis J, Keller G. 2004. Haemangioblast commitment is initiated in the primitive streak of the mouse embryo. *Nature* **432:** 625–630.

Kinder SJ, Tsang TE, Quinlan GA, Hadjantonakis AK, Nagy A, Tam PP. 1999. The orderly allocation of mesodermal cells to the extraembryonic structures and the anteroposterior axis during gastrulation of the mouse embryo. *Development* **126:** 4691–4701.

Kondo M, Weissman IL, Akashi K. 1997. Identification of clonogenic common lymphoid progenitors in mouse bone marrow. *Cell* **91:** 661–672.

Lawson KA, Meneses JJ, Pedersen RA. 1991. Clonal analysis of epiblast fate during germ layer formation in the mouse embryo. *Development* **113:** 891–911.

Lee G, Lo A, Short SA, Mankelow TJ, Spring F, Parsons SF, Yazdanbakhsh K, Mohandas N, Anstee DJ, Chasis JA. 2006. Targeted gene deletion demonstrates that the cell adhesion molecule ICAM-4 is critical for erythroblastic island formation. *Blood* **108:** 2064–2071.

Lenox LE, Perry JM, Paulson RF. 2005. BMP4 and Madh5 regulate the erythroid response to acute anemia. *Blood* **105:** 2741–2748.

Libregts SF, Gutierrez L, de Bruin AM, Wensveen FM, Papadopoulos P, van Ijcken W, Ozgur Z, Philipsen S, Nolte MA. 2011. Chronic IFN-γ production in mice induces anemia by reducing erythrocyte life span and inhibiting erythropoiesis through an IRF-1/PU.1 axis. *Blood* **118:** 2578–2588.

Lin CS, Lim SK, D'Agati V, Costantini F. 1996. Differential effects of an erythropoietin receptor gene disruption on primitive and definitive erythropoiesis. *Genes Dev* **10:** 154–164.

Liu Y, Pop R, Sadegh C, Brugnara C, Haase VH, Socolovsky M. 2006. Suppression of Fas–FasL coexpression by erythropoietin mediates erythroblast expansion during the erythropoietic stress response in vivo. *Blood* **108:** 123–133.

Lux CT, Yoshimoto M, McGrath K, Conway SJ, Palis J, Yoder MC. 2007. All primitive and definitive hematopoietic progenitor cells emerging prior to E10 in the mouse embryo are products of the yolk sac. *Blood* **111:** 3435–3438.

Manz MG, Miyamoto T, Akashi K, Weissman IL. 2002. Prospective isolation of human clonogenic common myeloid progenitors. *Proc Natl Acad Sci* **99:** 11872–11877.

Martin C, Beaupain D, Dieterlen-Lievre F. 1978. Developmental relationships between vitelline and intra-embryonic haemopoiesis studied in avian "yolk sac chimaeras." *Cell Differ* **7:** 115–130.

Mathias LA, Fisher TC, Zeng L, Meiselman HJ, Weinberg KI, Hiti AL, Malik P. 2000. Ineffective erythropoiesis in β-thalassemia major is due to apoptosis at the polychromatophilic normoblast stage. *Exp Hematol* **28:** 1343–1353.

McGrath KE, Palis J. 2005. Hematopoiesis in the yolk sac: More than meets the eye. *Exp Hematol* **33:** 1021–1028.

Medvinsky A, Dzierzak E. 1996. Definitive hematopoiesis is autonomously initiated by the AGM region. *Cell* **86:** 897–906.

Menon MP, Karur V, Bogacheva O, Bogachev O, Cuetara B, Wojchowski DM. 2006. Signals for stress erythropoiesis are integrated via an erythropoietin receptor–phosphotyrosine-343–Stat5 axis. *J Clin Invest* **116:** 683–694.

Menzel S, Garner C, Gut I, Matsuda F, Yamaguchi M, Heath S, Foglio M, Zelenika D, Boland A, Rooks H, et al. 2007. A QTL influencing F cell production maps to a gene encoding a zinc-finger protein on chromosome 2p15. *Nat Genet* **39:** 1197–1199.

Migliaccio AR, Campisi S, Migliaccio G. 2001. Standardization of progenitor cell assay for cord blood banking. *Ann Ist Super Sanita* **37:** 595–600.

Migliaccio G, Di Pietro R, di Giacomo V, Di Baldassarre A, Migliaccio AR, Maccioni L, Galanello R, Papayannopoulou T. 2002. In vitro mass production of human erythroid cells from the blood of normal donors and of thalassemic patients. *Blood Cells Mol Dis* **28:** 169–180.

Miller IJ, Bieker JJ. 1993. A novel, erythroid cell-specific murine transcription factor that binds to the CACCC element and is related to the Kruppel family of nuclear proteins. *Mol Cell Biol* **13:** 2776–2786.

Moore MA, Metcalf D. 1970. Ontogeny of the haemopoietic system: Yolk sac origin of in vivo and in vitro colony forming cells in the developing mouse embryo. *Br J Haematol* **18:** 279–296.

Muller AM, Medvinsky A, Strouboulis J, Grosveld F, Dzierzak E. 1994. Development of hematopoietic stem cell activity in the mouse embryo. *Immunity* **1:** 291–301.

Murray P. 1932. The development in vitro of the blood of the early chick embryo. *Proc Roy Soc London* **11:** 497–521.

Neildez-Nguyen TM, Wajcman H, Marden MC, Bensidhoum M, Moncollin V, Giarratana MC, Kobari L, Thierry D, Douay L. 2002. Human erythroid cells produced ex vivo at large scale differentiate into red blood cells in vivo. *Nat Biotechnol* **20:** 467–472.

Nerlov C, Graf T. 1998. PU.1 induces myeloid lineage commitment in multipotent hematopoietic progenitors. *Genes Dev* **12:** 2403–2412.

North TE, de Bruijn MF, Stacy T, Talebian L, Lind E, Robin C, Binder M, Dzierzak E, Speck NA. 2002. Runx1 expression marks long-term repopulating hematopoietic stem cells in the midgestation mouse embryo. *Immunity* **16:** 661–672.

Nuez B, Michalovich D, Bygrave A, Ploemacher R, Grosveld F. 1995. Defective haematopoiesis in fetal liver resulting from inactivation of the EKLF gene. *Nature* **375:** 316–318.

Okuda T, van Deursen J, Hiebert SW, Grosveld G, Downing JR. 1996. AML1, the target of multiple chromosomal translocations in human leukemia, is essential for normal fetal liver hematopoiesis. *Cell* **84:** 321–330.

Olivier EN, Qiu C, Velho M, Hirsch RE, Bouhassira EE. 2006. Large-scale production of embryonic red blood cells from human embryonic stem cells. *Exp Hematol* **34:** 1635–1642.

Orkin SH, Antonarakis SE, Kazazian HH Jr. 1984. Base substitution at position −88 in a β-thalassemic globin gene. Further evidence for the role of distal promoter element ACACCC. *J Biol Chem* **259:** 8679–8681.

Ottersbach K, Dzierzak E. 2005. The murine placenta contains hematopoietic stem cells within the vascular labyrinth region. *Dev Cell* **8:** 377–387.

Papadaki HA, Kritikos HD, Valatas V, Boumpas DT, Eliopoulos GD. 2002. Anemia of chronic disease in rheumatoid arthritis is associated with increased apoptosis of bone marrow erythroid cells: Improvement following anti-tumor necrosis factor-α antibody therapy. *Blood* **100:** 474–482.

Papayannopoulou T, Brice M, Stamatoyannopoulos G. 1977. Hemoglobin F synthesis in vitro: Evidence for control at the level of primitive erythroid stem cells. *Proc Natl Acad Sci* **74:** 2923–2927.

Park C, Ma YD, Choi K. 2005. Evidence for the hemangioblast. *Exp Hematol* **33:** 965–970.

Perkins AC, Sharpe AH, Orkin SH. 1995. Lethal β-thalassaemia in mice lacking the erythroid CACCC-transcription factor EKLF. *Nature* **375:** 318–322.

Perkins AC, Peterson KR, Stamatoyannopoulos G, Witkowska HE, Orkin SH. 2000. Fetal expression of a human Aγ globin transgene rescues globin chain imbalance but not hemolysis in EKLF null mouse embryos. *Blood* **95:** 1827–1833.

Perseu L, Satta S, Moi P, Demartis FR, Manunza L, Sollaino MC, Barella S, Cao A, Galanello R. 2011. KLF1 gene mutations cause borderline HbA(2). *Blood* **118:** 4454–4458.

Peterson KR, Li QL, Clegg CH, Furukawa T, Navas PA, Norton EJ, Kimbrough TG, Stamatoyannopoulos G. 1995. Use of yeast artificial chromosomes (YACs) in studies of mammalian development: Production of β-globin locus YAC mice carrying human globin developmental mutants. *Proc Natl Acad Sci* **92:** 5655–5659.

Pilat S, Carotta S, Schiedlmeier B, Kamino K, Mairhofer A, Will E, Modlich U, Steinlein P, Ostertag W, Baum C, et al. 2005. HOXB4 enforces equivalent fates of ES-cell-derived and adult hematopoietic cells. *Proc Natl Acad Sci* **102:** 12101–12106.

Pilon AM, Arcasoy MO, Dressman HK, Vayda SE, Maksimova YD, Sangerman JI, Gallagher PG, Bodine DM. 2008. Failure of terminal erythroid differentiation in EKLF-deficient mice is associated with cell cycle perturbation and reduced expression of E2F2. *Mol Cell Biol* **28:** 7394–7401.

Pootrakul P, Sirankapracha P, Hemsorach S, Moungsub W, Kumbunlue R, Piangitjagum A, Wasi P, Ma L, Schrier SL. 2000. A correlation of erythrokinetics, ineffective erythropoiesis, and erythroid precursor apoptosis in Thai patients with thalassemia. *Blood* **96:** 2606–2612.

Porcher C, Swat W, Rockwell K, Fujiwara Y, Alt FW, Orkin SH. 1996. The T cell leukemia oncoprotein SCL/tal-1 is essential for development of all hematopoietic lineages. *Cell* **86:** 47–57.

Ribeil JA, Zermati Y, Vandekerckhove J, Cathelin S, Kersual J, Dussiot M, Coulon S, Moura IC, Zeuner A, Kirkegaard-Sorensen T, et al. 2007. Hsp70 regulates erythropoiesis by preventing caspase-3-mediated cleavage of GATA-1. *Nature* **445:** 102–105.

Robb L, Lyons I, Li R, Hartley L, Kontgen F, Harvey RP, Metcalf D, Begley CG. 1995. Absence of yolk sac hematopoiesis from mice with a targeted disruption of the *scl* gene. *Proc Natl Acad Sci* **92:** 7075–7079.

Robb L, Elwood NJ, Elefanty AG, Kontgen F, Li R, Barnett LD, Begley CG. 1996. The *scl* gene product is required for the generation of all hematopoietic lineages in the adult mouse. *EMBO J* **15:** 4123–4129.

Russell ES, Bernstein SE. 1966. Blood and blood formation. In *Biology of the laboratory mouse* (ed. Green EL), pp. 351–372. McGraw-Hill, New York.

Sabin F. 1920. *Studies on the origin of blood vessels and of red blood corpuscles as seen in the living blastoderm of chicks during the second day of incubation*, Vol. 9, p. 214. Carnegie Institute of Washington, Washington, DC.

* Sankaran VG, Orkin SH. 2013. The switch from fetal to adult hemoglobin. *Cold Spring Harb Perspect Med* **3:** a011643.

Sankaran VG, Menne TF, Xu J, Akie TE, Lettre G, Van Handel B, Mikkola HK, Hirschhorn JN, Cantor AB, Orkin SH. 2008. Human fetal hemoglobin expression is regulated by the developmental stage-specific repressor BCL11A. *Science* **322:** 1839–1842.

Scott EW, Simon MC, Anastasi J, Singh H. 1994. Requirement of transcription factor PU.1 in the development of multiple hematopoietic lineages. *Science* **265:** 1573–1577.

Scott LM, Priestley GV, Papayannopoulou T. 2003. Deletion of α4 integrins from adult hematopoietic cells reveals roles in homeostasis, regeneration, and homing. *Mol Cell Biol* **23:** 9349–9360.

Shalaby F, Rossant J, Yamaguchi TP, Gertsenstein M, Wu XF, Breitman ML, Schuh AC. 1995. Failure of blood-island formation and vasculogenesis in Flk-1-deficient mice. *Nature* **376:** 62–66.

Shivdasani RA, Mayer EL, Orkin SH. 1995. Absence of blood formation in mice lacking the T-cell leukaemia oncoprotein tal-1/SCL. *Nature* **373:** 432–434.

Singleton BK, Burton NM, Green C, Brady RL, Anstee DJ. 2008. Mutations in EKLF/KLF1 form the molecular basis of the rare blood group In(Lu) phenotype. *Blood* **112:** 2081–2088.

Socolovsky M. 2007. Molecular insights into stress erythropoiesis. *Curr Opin Hematol* **14:** 215–224.

Socolovsky M, Fallon AE, Wang S, Brugnara C, Lodish HF. 1999. Fetal anemia and apoptosis of red cell progenitors in Stat5a$^{-/-}$5b$^{-/-}$ mice: A direct role for Stat5 in Bcl-X(L) induction. *Cell* **98:** 181–191.

Socolovsky M, Nam H, Fleming MD, Haase VH, Brugnara C, Lodish HF. 2001. Ineffective erythropoiesis in Stat5a$^{-/-}$b$^{-/-}$ mice due to decreased survival of early erythroblasts. *Blood* **98:** 3261–3273.

Soni S, Bala S, Gwynn B, Sahr KE, Peters LL, Hanspal M. 2006. Absence of erythroblast macrophage protein (Emp) leads to failure of erythroblast nuclear extrusion. *J Biol Chem* **281:** 20181–20189.

Southwood CM, Downs KM, Bieker JJ. 1996. Erythroid Kruppel-like factor exhibits an early and sequentially localized pattern of expression during mammalian erythroid ontogeny. *Dev Dyn* **206:** 248–259.

Stamatoyannopoulos G. 2005. Control of globin gene expression during development and erythroid differentiation. *Exp Hematol* **33:** 259–271.

Strouboulis J, Dillon N, Grosveld F. 1992. Developmental regulation of a complete 70-kb human β-globin locus in transgenic mice. *Genes Dev* **6:** 1857–1864.

Tallack MR, Keys JR, Perkins AC. 2007. Erythroid Kruppel-like factor regulates the G1 cyclin dependent kinase inhibitor p18^{INK4c}. *J Mol Biol* **369:** 313–321.

Tavian M, Peault B. 2005. Embryonic development of the human hematopoietic system. *Int J Dev Biol* **49:** 243–250.

Tavian M, Hallais MF, Peault B. 1999. Emergence of intraembryonic hematopoietic precursors in the pre-liver human embryo. *Development* **126:** 793–803.

Tsai FY, Orkin SH. 1997. Transcription factor GATA-2 is required for proliferation/survival of early hematopoietic

cells and mast cell formation, but not for erythroid and myeloid terminal differentiation. *Blood* **89:** 3636–3643.

Tsai FY, Keller G, Kuo FC, Weiss M, Chen J, Rosenblatt M, Alt FW, Orkin SH. 1994. An early haematopoietic defect in mice lacking the transcription factor GATA-2. *Nature* **371:** 221–226.

Turpen JB, Knudson CM. 1982. Ontogeny of hematopoietic cells in *Rana pipiens*: Precursor cell migration during embryogenesis. *Dev Biol* **89:** 138–151.

Ueno H, Weissman IL. 2006. Clonal analysis of mouse development reveals a polyclonal origin for yolk sac blood islands. *Dev Cell* **11:** 519–533.

van den Akker E, Satchwell TJ, Pellegrin S, Daniels G, Toye AM. 2010. The majority of the in vitro erythroid expansion potential resides in $CD34^-$ cells, outweighing the contribution of $CD34^+$ cells and significantly increasing the erythroblast yield from peripheral blood samples. *Haematologica* **95:** 1594–1598.

Wanachiwanawin W, Wiener E, Siripanyaphinyo U, Chinprasertsuk S, Mawas F, Fucharoen S, Wickramasinghe SN, Pootrakul P, Visudhiphan S. 1999. Serum levels of tumor necrosis factor-α, interleukin-1, and interferon-γ in β^0-thalassemia/HbE and their clinical significance. *J Interferon Cytokine Res* **19:** 105–111.

Wood HB, May G, Healy L, Enver T, Morriss-Kay GM. 1997. CD34 expression patterns during early mouse development are related to modes of blood vessel formation and reveal additional sites of hematopoiesis. *Blood* **90:** 2300–2311.

Wu H, Klingmuller U, Besmer P, Lodish HF. 1995. Interaction of the erythropoietin and stem-cell-factor receptors. *Nature* **377:** 242–246.

Yokomizo T, Yamada-Inagawa T, Yzaguirre AD, Chen MJ, Speck NA, Dzierzak E. 2012. Whole-mount three-dimensional imaging of internally localized immunostained cells within mouse embryos. *Nat Protoc* **7:** 421–431.

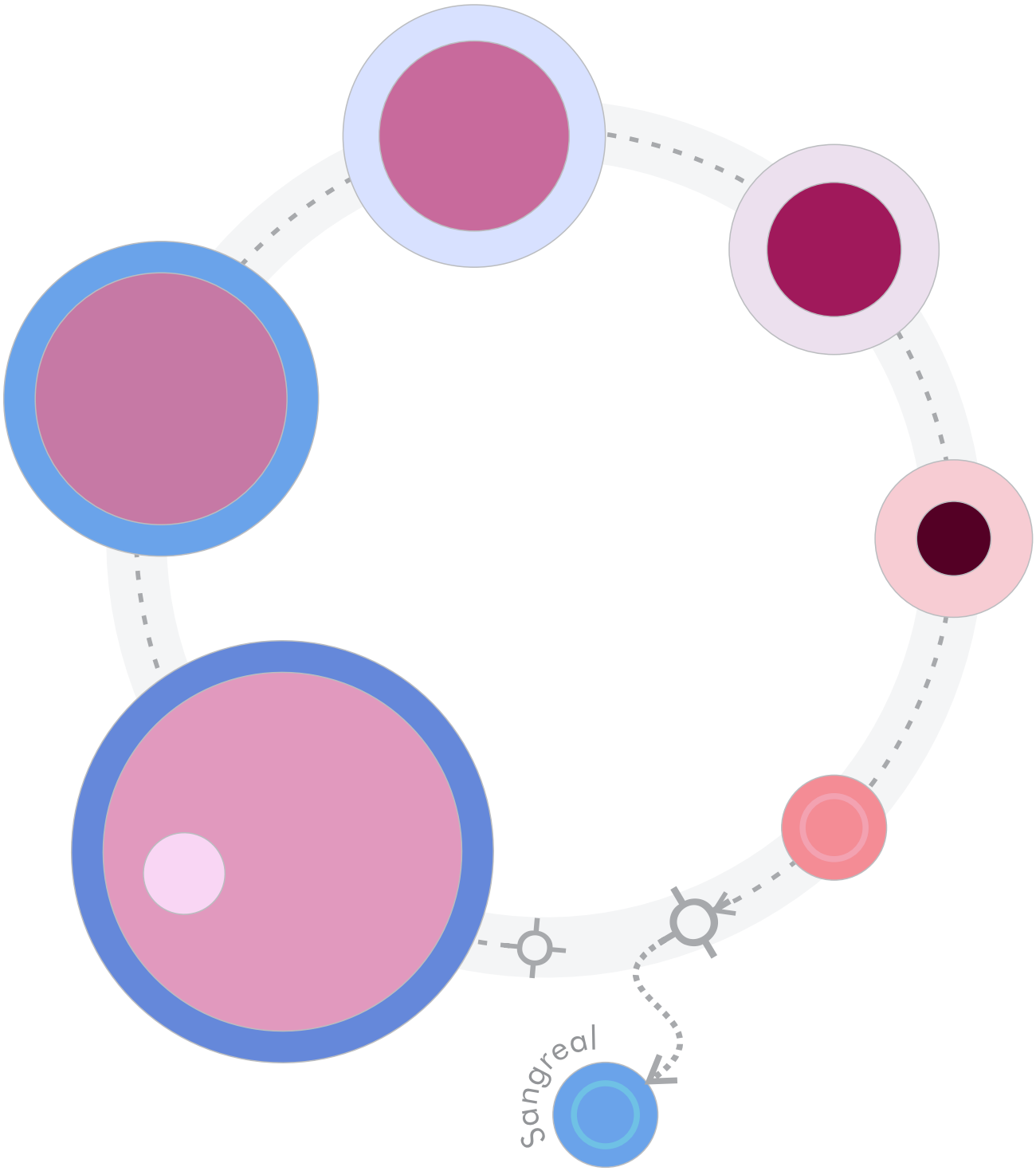
Yoshida H, Kawane K, Koike M, Mori Y, Uchiyama Y, Nagata S. 2005. Phosphatidylserine-dependent engulfment by macrophages of nuclei from erythroid precursor cells. *Nature* **437:** 754–758.

Zeigler BM, Sugiyama D, Chen M, Guo Y, Downs KM, Speck NA. 2006. The allantois and chorion, when isolated before circulation or chorio-allantoic fusion, have hematopoietic potential. *Development* **133:** 4183–4192.

Zeuner A, Eramo A, Testa U, Felli N, Pelosi E, Mariani G, Srinivasula SM, Alnemri ES, Condorelli G, Peschle C, et al. 2003. Control of erythroid cell production via caspase-mediated cleavage of transcription factor SCL/Tal-1. *Cell Death Differ* **10:** 905–913.

Zhou D, Pawlik KM, Ren J, Sun CW, Townes TM. 2006. Differential binding of erythroid Krupple-like factor to embryonic/fetal globin gene promoters during development. *J Biol Chem* **281:** 16052–16057.

Zhou D, Liu K, Sun CW, Pawlik KM, Townes TM. 2010. KLF1 regulates BCL11A expression and γ- to β-globin gene switching. *Nat Genet* **42:** 742–744.



BIOMIMETIC
ERYTHROPOIESIS

Irena Pangeršič