

PRODUKSJON AV BIOLOGISKE LEGEMIDLER OG VAKSINER I NORGE

Sintef sin satsing på bioteknologiske prosesser og nanoteknologi med relevans for norsk vaksine/legemiddel produksjon

v/Håvard Sletta, Forskningsleder, avd. Bioteknologi og nanoteknologi, Sintef Industri

SINTEF - organisasjon

 Helse og velferd i SINTEF
220 mill kr (2020)

Stiftelsen SINTEF

Institutter

SINTEF
Community

SINTEF
Industri

SINTEF
Digital

SINTEF
Ocean
(71,5%)

SINTEF
Energi
(61%)

SINTEF
Manufacturing
(50,1%)

Andre
datterselskaper

SINTEF
Nord

SINTEF
Ålesund

SINTEF
TTO

SINTEF
Helgeland
(56%)

SINTEF
Narvik
(66,66%)



Helsetjenester med digital støtte
E-helse, velferdsteknologi, helselogistikk



Digitale pasienter
Styrke pasientrollen gjennom teknologi



Teknologi i global helse



Framtidens medisinproduksjon

SINTEF Industri

Avdeling for Bioteknologi og Nanomedisin



Forskningsjef
Trond E. Ellingsen



Bioteknologi
Håvard Sletta



Massespektrometri
Sjoerd Hak



**Polymerpartikler og
overflatekemi**
Heidi Johnsen



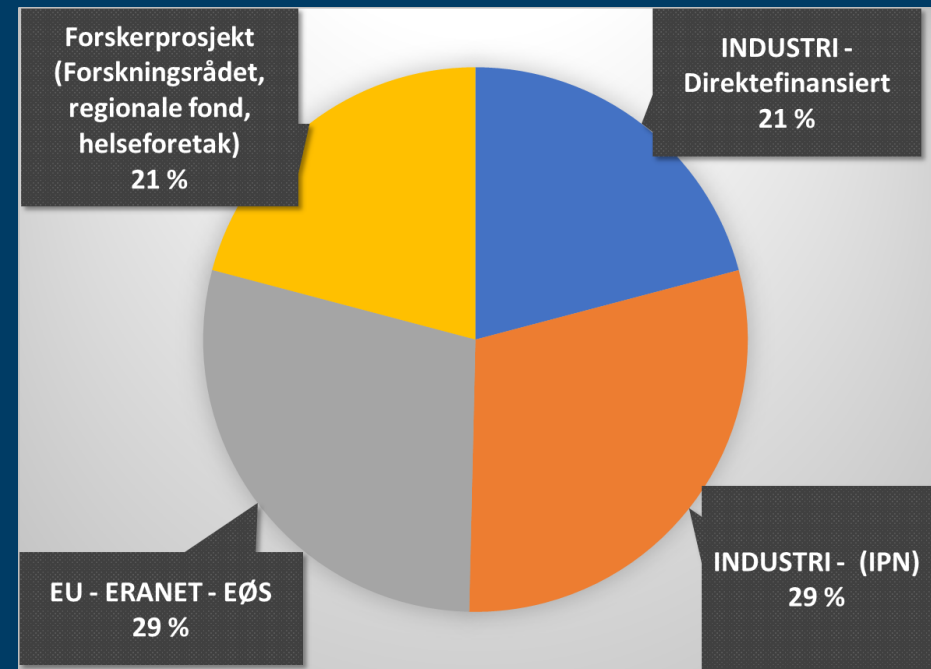
Norske og internasjonale
forskningsgrupper og industri

78 ansatte
120 prosjekter

Bioteknologiske prosesser og nanoteknologi med relevans for norsk vaksine/legemiddel produksjon

- Mer enn 30 år kompetanse innen feltet
- 60-70 % av vår virksomhet
- >80 pågående prosjekter (89 mill kr i 2020)

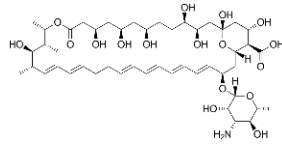
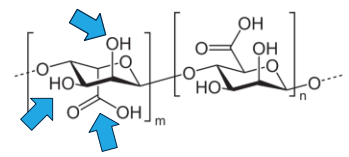
Eksternfinansierte prosjekter



Strategiske egenfinansierte prosjekter

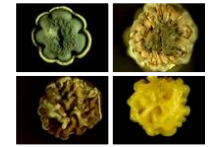
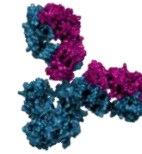
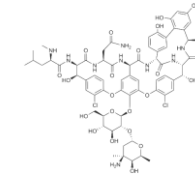
Tilpassede infrastrukturplattformer

Eksempler på infrastruktur og plattformer



Biofarmasøytika

Oppdagelse, skreddersøm, produksjon og karakterisering



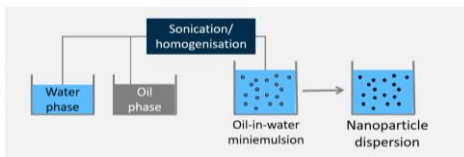
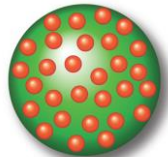
Bioprospektering

Stammeutvikling

Bioprosessutvikling

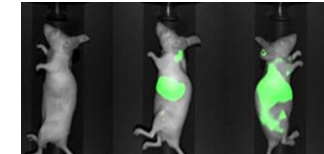
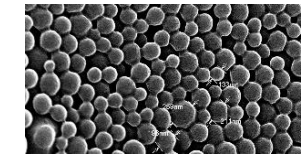
Oppskalert produksjon

Karakterisering



Nanomedisin

Innkapsling, karakterisering, *in vitro* testing og prekliniske studier



Nanoformulering av bioaktive stoffer

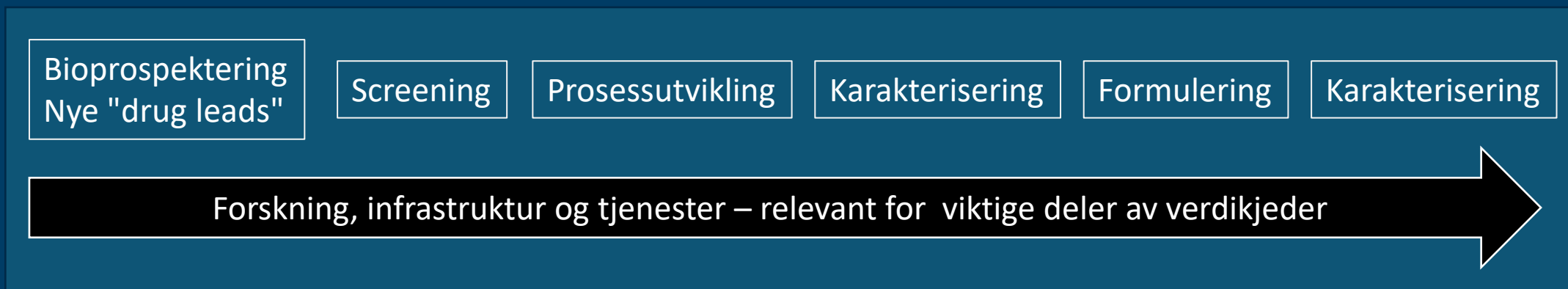
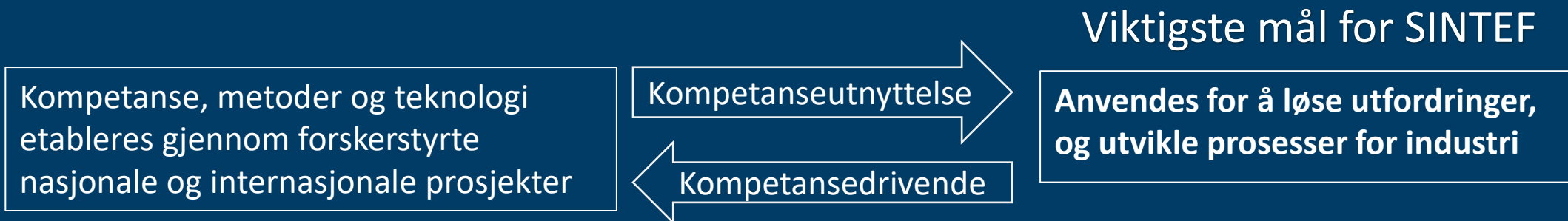
Fysiko-kjemisk karakterisering

In vitro toksisitet og effekt

Preklinisk testing



Arbeidsform og aktivitetsbeskrivelse



Industrisamarbeidspartnere: Fra oppstartselskaper til etablert industri (prosessutvikling)



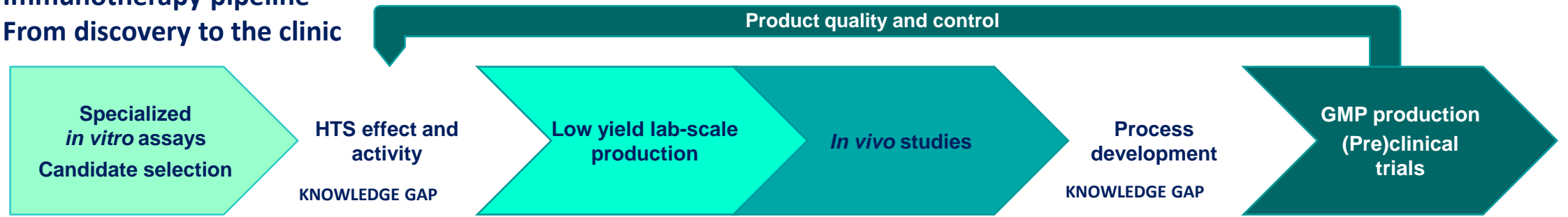
Relevante strategiske satsinger/prosjekter

- Område hvor vi mener det er viktig å etablere kompetanse for å kunne tilby ny kompetanse/teknologi basert på forventninger til et framtidig viktig marked
- Satsingene baseres på nettverksanalyser og kartlegging av reell interesse fra interessenter/samarbeidspartnere/industri
- Satsingene er (nesten) alltid basert på områder hvor vi kan utnytte/videreutvikle eksisterende infrastruktur og kompetanse
- Strategisk rekruttering er svært viktig for å etablere nye markedsområder

Internsatsning: Immunterapi : 12MNOK/4år

Mål: Å tette kunnskapsgap langs utviklingskjeden

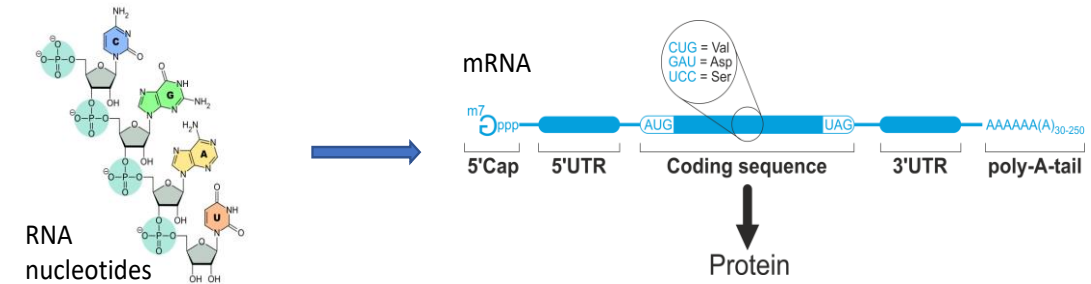
Immunotherapy pipeline
From discovery to the clinic



- Utvikler standardisert cellebasert assaypakke for immunotoksikologi og effekt av immunoterapeutiske legemidler ¹
- Dyremodeller for å vurdere effekt og sikkerhet av legemidler som påvirker immunsystemet
- Optimaliserer produksjonsprosesser og kvalitetskontroll for antistoff og cellebaserte terapier.

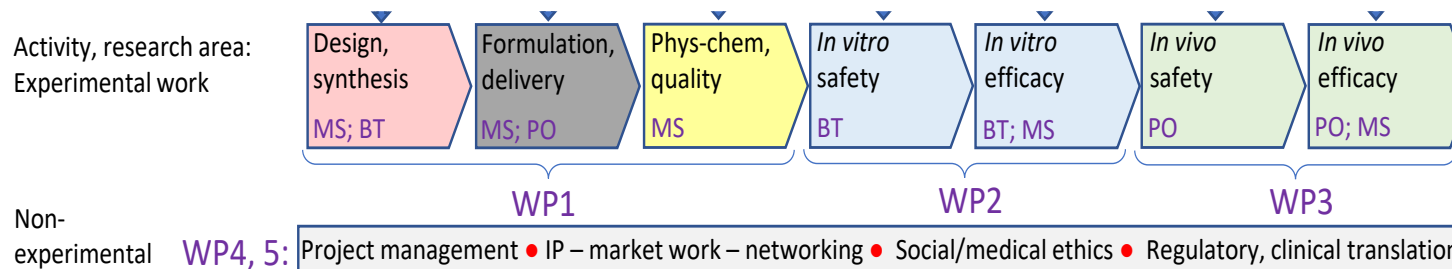
Internsatsing: mRNA basert terapi (13 mill/4 år)

- Få kroppen til å lage sine egne medisiner (proteiner) – *in vivo*
- Svært spesifikke, ingen/liten toksisitet
- Svært bredt spektrum av anvendelser (vaksiner, protein-reparasjon, regenerativ medisin, kreft, neurologiske, kardiovaskulære...)
 - Tre av de fremste Covid-19 vaksinekandidatene er mRNA i lipid-nanopartikler
- *Mål:* Etablere en komplett kompetanse- og mulighets-kjede i SINTEF på mRNA-terapi
- Et svært sterkt advisory board, som inkluderer
 - Industri: eTheRNA, Astra Zeneca
 - Klinikere (Global sarcoma alliance)
 - Store offentlige institusjoner: NIAID (NIH)
 - Norsk universitet (UiT)

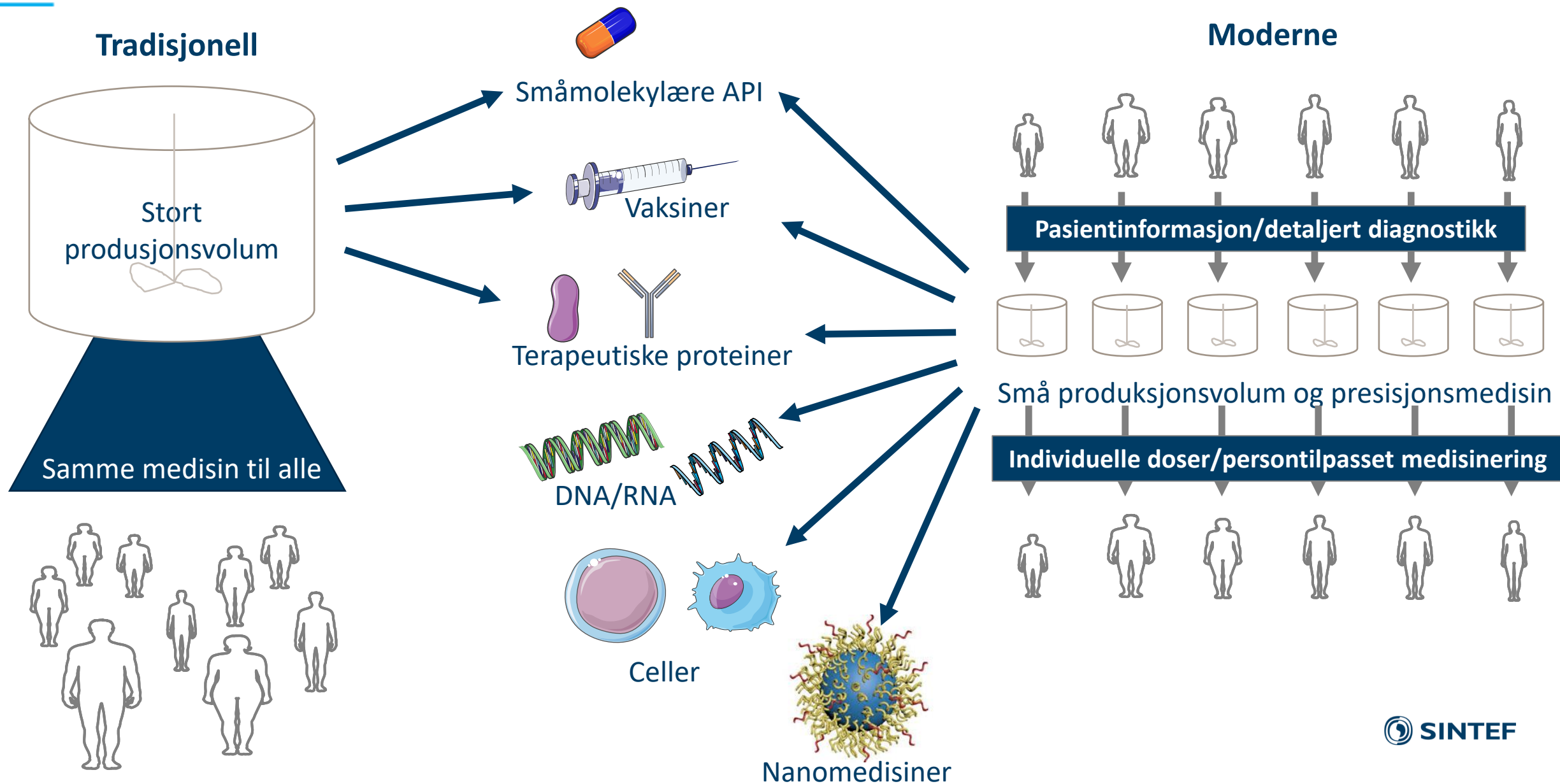


SINTEFs tilnærming:

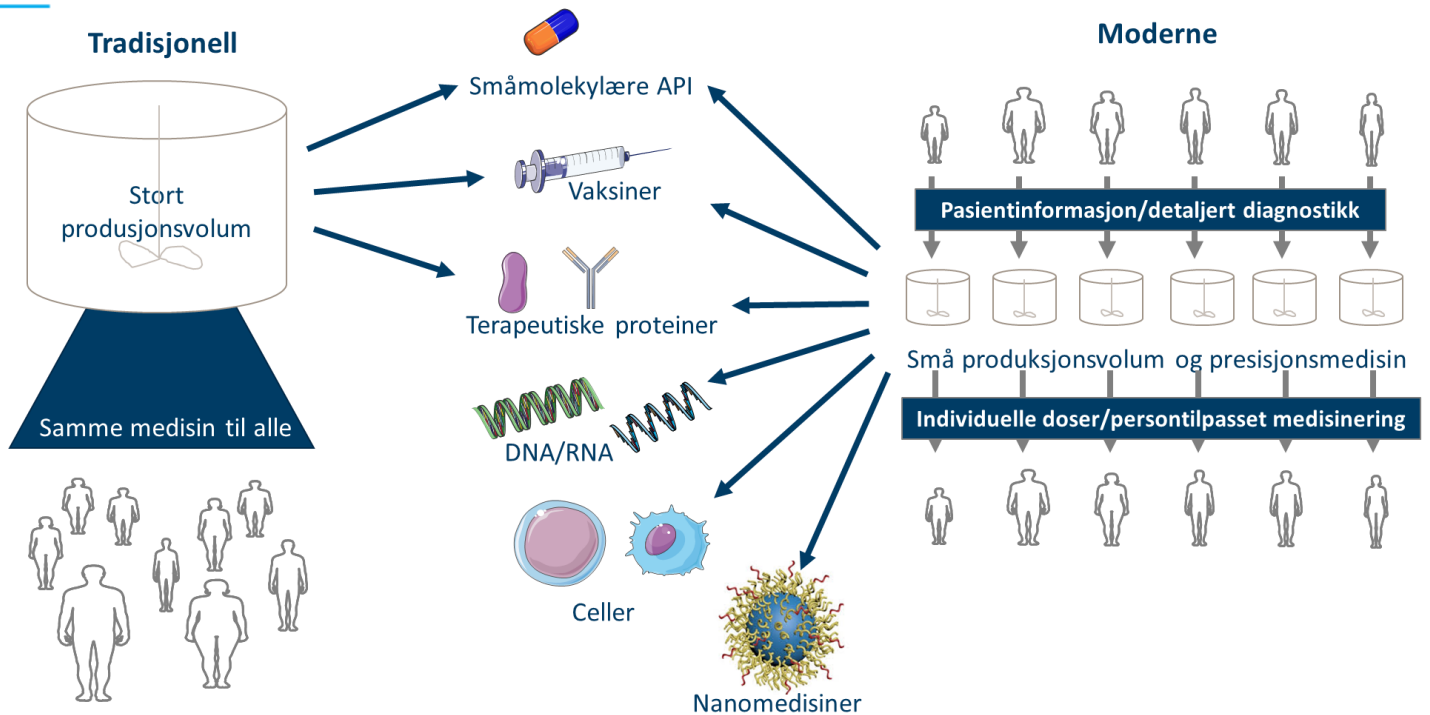
- (Nano)formulering og/eller karakterisering som en tjeneste
- Grunnforskning
- Målrettet utvikling for industripartnere
- Etikk: Delta og gi premisser i den offentlige debatten!



Nye (og tradisjonelle) behov innen medisinproduksjon



Nye (og tradisjonelle) behov innen medisinproduksjon



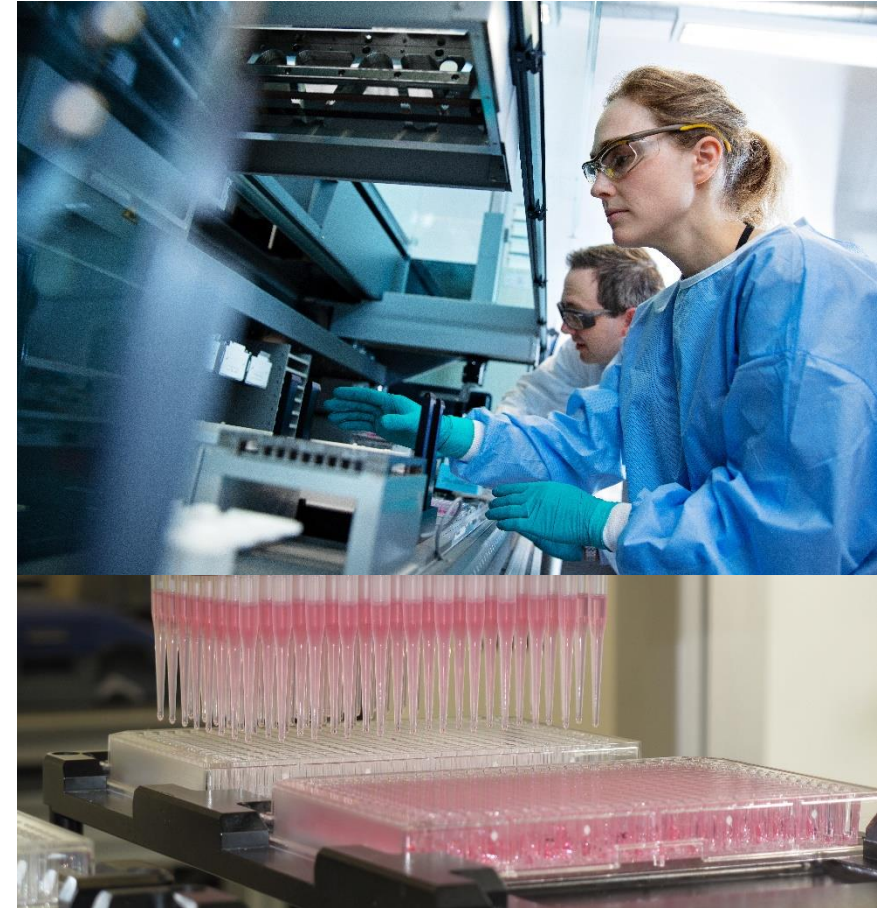
Mulighetsrom for en økt nasjonal legemiddelproduksjon (ny og etablert industri)

Infrastruktur og kompetanse

High-throughput screening plattform

- SINTEF har avansert infrastruktur for robotisert high throughput screening
- Integreerte state-of-the art deteksjonsteknologier
 - FACS
 - Konfokalmikroskop
 - State-of-the-art platelesere
 - High-throughput MS/MS
- **Behandler rutinemessig tusenvis av prøver på en gang.**
 - **Stort potensiale for kostnadsreduksjon i legemiddeltesting**

Partner i nasjonale og internasjonale forskningsinfrastrukturer:



High-throughput screening i legemiddeltesting

- Utvikling av nye legemidler ¹
 - Screening av kjemiske bibliotek for identifisering av nye drug leads
 - Identifisering av naturlige bioaktive forbindelser (bioprospektering)
- Høykapasitetsscreening av effekt og sikkerhet av legemidler ²
 - Endotoksin
 - Mykoplasma
 - Mikrobiell kontaminasjon
 - Fullrobotiserte protokoller for cellebasert testing av nanomedisiner i henhold til EUNCL/NCI-NCL SOP'er
- Effektstudier i celle- og bakteriekultur ^{3,4}
 - Biofilm
 - Kombinatorisk legemiddelscreening
 - Persontilpasset medisin





Bioprosessutvikling (2020)

Fermenteringsprosess utvikling (1ml – 200-l)

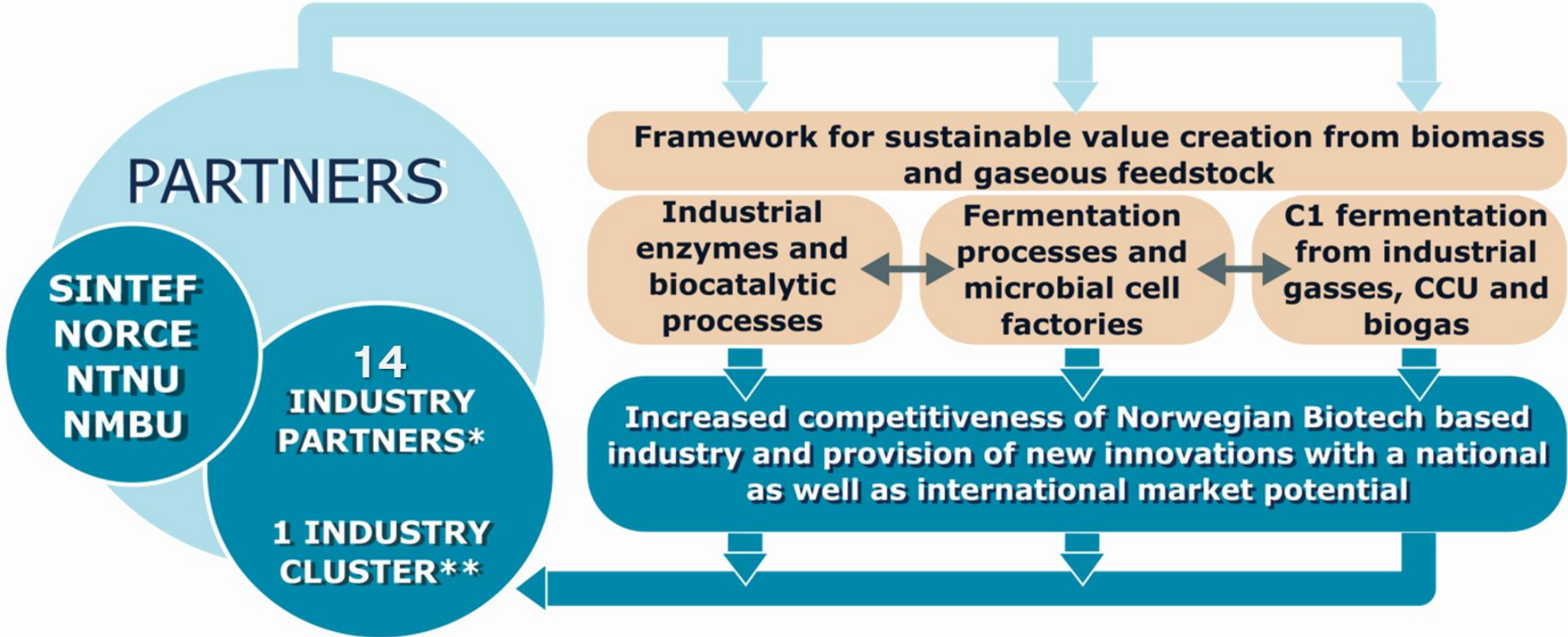
- Antibiotika
- Steroider
- Antistoff
- DNA-vektorer
- Enzymer (diagnostikk)
- Biopolymere (og oligomere)
- Fiskevaksiner

Bakterier, gjær, sopp og mammalske celler

Stammeutvikling:

Klassisk mutagenese og screening → CRISPR

SFI Industrial Biotechnology



SFI –IB 214 mill/8 år

Massespektrometri



Instruments:

- 3 x GC-MS (identification of unknowns)
- 2 x GC-MS/MS (secure, highly sensitive)
- 4 x LC-MS (all-round)
- 9 x LC-MS/MS (secure, highly sensitive)
- 2 x LC-QTOF-MS/MS (secure, larger molecules)
- 1 x FT-ICR-MS (ultra-high resolution, identification in extremely complex media)
- 2 x MALDI TOF/TOF-MS (MS Imaging)
- 1 x Field flow fractionation (FFF) (particles, polymers)
- 1 x ICP-MS/MS (inorganic compounds, highly sensitive)
- RapidFire (> 10000 analyses/day)
- SEC/GPC (particle size)
- HPLC (analytical and preparative)

Specific compound classes:

- Proteins
- Amino acids
- Lipids
- Dioxins
- Dibenzofuranes
- PCB (Polychlorinated biphenyls)
- Heavy metals
- Elements (most of the periodic table)
- Rare earth elements
- Organic anions
- Amines
- Pharmaceuticals
- Biopharmaceuticals
- Toxins
- PAH (Polycyclic Aromatic hydrocarbons)
- Antioxidants

In addition unspecific analysis:

- Identification of unknown organic compounds by GC-MS
- Identification of organic compounds by LC-QTOF and FT-ICR-MS (elemental formula)
- Identification of inorganic compounds by ICP-MS
- Characterization bio-based products by FT-ICR-MS
- Size characterization by GPC/SEC (Gel Permeation Chromatography/Size Exclusion Chromatography) and FFF (Field Flow Fractionation)
- Characterization of nanoparticles (size, shape and element composition)
- Characterization of other particles and polymers
- Identification of process related compounds (including bio-based)
- Odorous and taste related compounds (of microbiological and other origin)

+++

Nanomedisin i SINTEF

Kompetanse

Nanoformulering



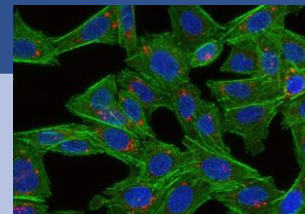
Materialteknologi



Fysisk-kjemisk karakterisering



In vitro studier



In vivo studier



Strategiske satsningsområder

Kreftbehandling

Vaksiner

Tarm mikrobiota

Oppskalering og produksjon

Safety



Industripartnere



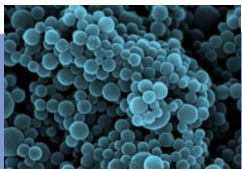
stryker®



AlgiPharma



Tilgjengelig infrastruktur for nanomedisin



Syntese/fremstilling

- Nanomedisinlab for arbeid med legemidler under sterile forhold
- Synteselaber for nanomaterialer
- MiNaLab (lab-on-a-chip/lab-on-a-disc produksjon)
- 3D (bio)printing
- Ultracentrifuge
- Fermenteringslaboratorium
- Utstyr for opparbeiding/opprensing av nanopartikler
- Mikrokanalsystemer for partikkelsyntese

Van der Meel, R. et al. Nature Nanotechnology 14(11) (2019).

Åslund A. et al. Molecular Pharmaceutics 14 (8) (2017)



Fysisk-kjemisk karakterisering

- Nanoparticle Tracking Analysis (NTA)
- Platelesere
- IR
- qNano
- Zetasizer
- Field Flow Fractionation
- Elektronmikroskopi
- SAXS, XPS, FIB for overflateanalyser
- Massespektrometri-baserte metoder: FTICR-MS, QToF-MS, MS/MS, ICP-MS
- ^1H , ^{13}C and ^{31}P -NMR
- Size Exclusion Chromatography
- HPLC/GC

Prina-Mello, A. et al. Correspondence in Nature Nanotechnology, 14 (2019).

Borgos, S.E.F, in Pharmaceutical Nanotechnology: Innovation and Production, Vol. 1 (2016).



In vitro karakterisering

- High throughput-væskehåndtering og nanoliter væskedeposering
- Spektrofotometriske avlesningsmetoder
- Konfokal mikroskopi for brønnplater med automatisert bildeanalyse
- Flowcytometri med celledatering
- Robotiserte antistoffbaserte avlesningsmetoder

Sulheim, E. et al. International Journal of Molecular Sciences 18(11) (2017).



Dyrestudier

- Dyrestall
- MRI/PET
- Optisk heldyrsavbildning
- Ultralydabildning
- Utstyr for ultralydbehandling
- Utstyr for snitting av vev og avbildning
- Fotoakustisk avbildning

Snipstad, S. et al. Ultrasound in Medicine & Biology, 43(11) (2017).

Sulheim, E. et al. Nanotheranostics 3(1) (2019).

Roller



Infrastruktur
nanomedisinkarakterisering



ETPN (Ruth Schmid, Chair)



COST Action Nano2Clinic



EARTO WG Healthtech



SINTEF-Internt
Konsernsatsing Helse & Velferd

Oppsummert

- Vår målsetning er å kunne tilby ny og etablert industri relevant kompetanse og bistå til kostnadseffektiv prosessutvikling
- Vi har etablerte infrastrukturplattformer som er tilpasset for å løse små og store oppgaver knyttet til legemiddelutvikling
- Kompetanse og infrastruktur utvikles kontinuerlig for å tilpasse våre tjenester til nye markedsområder, både gjennom egenfinansierte strategiske satsinger og som partner/leder i nasjonale og internasjonale prosjekter
- Vi har svært lang erfaring med å jobbe med farmasøytisk industri
- Kompetanse er dokumentert både gjennom industrinettverk og vitenskapelig publisering i anerkjente tidsskrift



Technology for a better society

2020

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- Folkesson E, Niederdrofer B, Nakstad VT, Thommesen L, Klinkenberg G, Lægred A, Flobak Å (2020) High-throughput screening reveals higher synergistic effect of MEK inhibitor combinations in colon cancer spheroids. Nature Research
- Öztürk E, Stauber T, Levinson C, Cavalli E, Arlov Ø, Zenobi-Wong M (2020) Tyrosinase-crosslinked, tissue adhesive and biomimetic alginate sulfate hydrogels for cartilage repair. Biomed Mater. 15: 045019
- Fagerland SMT, Berg S, Hill DK, Snipstad S, Sulheim E, Hyldebakk A, Kim J, Davies CDL (2020) Ultrasound-mediated delivery of chemotherapy into the transgenic adenocarcinoma of the mouse prostate model. Ultrasound in Med & Biol
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